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**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

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GILEAD SCIENCES, INC., HOFFMANN-La ROCHE :
INC., F. HOFFMANN-La ROCHE LTD. and :
GENENTECH, INC., :
Plaintiffs, : Civil Action No. _____
v. :
NATCO PHARMA LIMITED and NATCO PHARMA :
INC., :
Defendants.
-----x

Plaintiffs, Gilead Sciences, Inc., Hoffmann-La Roche Inc., F. Hoffmann-La Roche Ltd. and Genentech, Inc. (collectively “Plaintiffs”), for their Complaint against Defendants, Natco Pharma Limited (“Natco Ltd.”) and Natco Pharma Inc. (“Natco Inc.”) (collectively “Natco”), to the best of their knowledge, information and belief, hereby allege as follows:

NATURE OF THE ACTION

1. This is an action for infringement of United States Patent No. 5,763,483 (“the '483 Patent”). Plaintiffs institute this action to enforce their patent rights covering Tamiflu® oseltamivir phosphate capsules 30 mg and 45 mg dosage forms, that are approved in the United States by the U.S. Food and Drug Agency (“FDA”) for the treatment of uncomplicated acute illness due to influenza infection in patients one year or older who have been symptomatic for no more than two days and for the prophylaxis of influenza in patients one year or older. Plaintiffs have instituted a related action in this Court to enforce their patent rights under the '483 patent with respect to the 75 mg dosage forms of oseltamivir phosphate in a Complaint filed March 15, 2011.

PARTIES

2. Plaintiff Gilead Sciences, Inc. is a company organized and existing under the laws of the State of Delaware with its principal place of business at 333 Lakeside Drive, Foster City, California 94404.

3. Plaintiff Hoffmann-La Roche Inc. is a company organized and existing under the laws of the State of New Jersey with its principal place of business at 340 Kingsland Street, Nutley, New Jersey 07110.

4. Plaintiff F. Hoffmann-La Roche Ltd. is a company organized and existing under the laws of Switzerland with its principal place of business at CH 4070 Basel, Switzerland.

5. Plaintiff Genentech, Inc. is a company organized and existing under the laws of the State of Delaware with its principal place of business at 1 DNA Way, South San Francisco, California 94080-4990.

6. Upon information and belief, Defendant Natco Ltd. is a corporation organized and existing under the laws of India and has a principal place of business at Natco House, Road No. 2, Banjara Hills, Hyderabad - 500 033, India.

7. On information and belief, Natco Ltd. is registered to do business in New Jersey and has a registered agent therein.

8. On information and belief, Natco Ltd. is developing generic drug products for sale and use throughout the United States, including within this judicial district.

9. On information and belief, Defendant Natco Inc. is a Delaware corporation having a principal place of business at 297 Mine Bank Road, Wellsville, Pennsylvania 17365-9514.

10. On information and belief, Natco Inc. is controlled and/or dominated by Natco Ltd.

11. On information and belief, Natco Inc. is a wholly owned subsidiary of Natco Ltd.

12. On information and belief, Natco Inc. is registered to do business in New Jersey and has a registered agent therein.

13. On information and belief, Natco Inc. is developing generic drug products for sale and use throughout the United States, including within this judicial district.

JURISDICTION AND VENUE

14. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202.

15. Natco Ltd. and Natco Inc. maintain a website at the uniform resource locator (URL) <http://www.natcopharma.co.in> ("the Natco website"), which serves as the website for

Natco. According to the website, Natco is in the business of “Research, Developing, Manufacturing and Marketing of Pharmaceutical Substances and Finished Dosage forms.”

16. On information and belief, Natco Ltd., independently and with the assistance and/or at the direction of Natco Inc., is developing generic drug products for sale and use throughout the United States, including within this judicial district.

17. On information and belief, Natco Inc., independently and with the assistance and/or at the direction of Natco Ltd., is developing generic drug products for sale and use throughout the United States, including within this judicial district.

18. On information and belief, Natco Ltd. and Natco Inc. operate as an integrated, unitary business. For example, in a January 14, 2011 press release available at the Natco website at http://www.natcopharma.co.in/k_and_c.html, Natco Ltd. states that Natco Inc. is a “wholly owned subsidiary.” Additionally, in a 2011 Bloomberg Law Company Report for Natco Ltd., Natco Inc. is listed as a subsidiary.

19. On information and belief, Natco Ltd. and Natco Inc. acted in concert to develop the Natco generic copies of Plaintiff’s Tamiflu® oseltamivir phosphate tablets (30 mg and 45 mg), and to seek approval from the FDA to sell Natco’s generic copies of plaintiff’s Tamiflu® oseltamivir phosphate tablets (30 mg and 45 mg) throughout the United States and in this judicial district.

20. On information and belief, Natco Ltd. has availed itself of the laws of the State of New Jersey and engaged in a course of conduct in the State of New Jersey, at least by identifying Nehru Gaddipati, 37 Veronica Ave, Somerset, New Jersey 08873-6800, as the registered agent of Natco Ltd.

21. On information and belief, Natco Ltd. has previously been sued in this district and has not challenged personal jurisdiction. *See, e.g., Celgene Corp. v. Natco Pharma Ltd.* (D.N.J. No. 2:10-cv-5197 (SDW/MCA)).

22. Further evidencing that jurisdiction over Natco Ltd. is proper in this jurisdiction, upon information and belief, Natco Ltd. has partnered with Alvogen Inc. (“Alvogen”), a pharmaceutical company based at Nine Campus Drive, Parsippany, New Jersey 07054 to market Natco’s generic copy of Plaintiffs’ Tamiflu® product. Upon information and belief, this partnership was reported in a September 2, 2011 press release at the Alvogen website at <http://www.alvogen.com/NewsMedia/ViewNews/alvogenandnatcosecurefirsttostatusongenericeversionoftamiflu>, where Alvogen states that “its India-based partner, Natco Pharma Limited, has filed an Abbreviated New Drug Application (ANDA) with the U.S. Food and Drug Administration (FDA for the generic version of Tamiflu® (oseltamivir phosphate).” Similarly, a February 9, 2011 press release at the Natco website at <http://www.natcopharma.co.in/tamiflu.html>, is titled “NATCO files ANDA for Oseltamivir, (Tamiflu®) ties up with Alvogen.”

23. On information and belief, by virtue of, *inter alia*, Natco Ltd.’s continuous and systematic contacts with New Jersey, including but not limited to the above-described contacts, this Court has general and specific personal jurisdiction over Natco Ltd. These activities satisfy due process and confer personal jurisdiction over Natco Ltd. consistent with New Jersey law.

24. On information and belief, as previously noted, Natco Inc. is a wholly owned subsidiary of Natco Ltd. On information and belief, by virtue of, *inter alia*, Natco Inc.’s relationship with Natco Ltd. in connection with the preparation and/or filing of ANDA No. 202-595, and the associated systematic and continuous activities within the state of New Jersey,

including but not limited to the development of generic drug products for sale to residents of New Jersey, this Court has personal jurisdiction over Natco Inc.

25. On information and belief, Natco Ltd., directly and/or through their agent, Natco Inc., caused tortious injury in New Jersey to Plaintiff Hoffmann-La Roche., Inc. a New Jersey Corporation, by filing ANDA No. 202-595, further supporting specific and/or general jurisdiction over Natco Ltd. and Natco Inc.

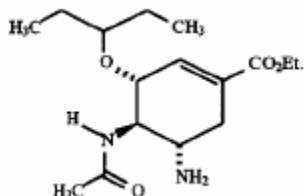
26. Venue is proper in this district under 28 U.S.C. §§ 1391 and 1400(b).

BACKGROUND

27. Hoffmann-La Roche Inc. is the holder of New Drug Application (“NDA”) No. 21-087 which relates to, *inter alia*, capsules containing 30 mg and 45 mg of oseltamivir phosphate formulated as the Tamiflu® brand for the treatment of uncomplicated acute illness due to influenza infection in patients one year or older who have been symptomatic for no more than two days and for the prophylaxis of influenza in patients one year or older. On July 2, 2007, the FDA approved plaintiffs’ Tamiflu® oseltamivir phosphate 30 mg and 45 mg drug products for marketing in the United States pursuant to section 505(b) of the Federal Food, Drug, and Cosmetics Act, (“FFDCA”), 21 U.S.C. § 355(b).

28. Gilead Sciences, Inc. is the owner of the '483 Patent (copy attached as Exhibit A), titled “Carbocyclic Compounds,” which was duly and legally issued by the United States Patent and Trademark Office on June 9, 1998.

29. The '483 Patent claims a compound having the following chemical structure:



, which is the active ingredient in the Tamiflu® product described in NDA No. 21-087, as well as methods for the treatment or prophylaxis of influenza infection using such a compound.

30. The '483 Patent expires on December 27, 2016, with an extension to June 27, 2017 due to pediatric exclusivity, as reflected in the publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations," (commonly referred to as the "Orange Book").

31. Hoffmann-La Roche Inc., F. Hoffmann-La Roche Ltd. and Genentech, Inc. are the exclusive licensees of the '483 Patent.

32. This action arises because of Natco's efforts to gain approval from the FDA to market generic copies of Plaintiffs' Tamiflu® oseltamivir phosphate 30 mg and 45 mg drug products prior to the expiration of patent rights covering same.

33. With passage of the Hatch-Waxman Act in 1984, the FFDCA provisions with respect to the generic drug approval process were amended in several important respects. One provision requires innovator drug companies to submit patent information to the FDA "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1). The FDA then lists the patent information in the "Orange Book."

34. Plaintiffs submitted patent information to the FDA in connection with NDA No. 21-087 Tamiflu® oseltamivir phosphate drug products, and the FDA has published the same for the 30 mg and 45 mg dosage forms in the Orange Book.

35. The Hatch-Waxman Act further amended the FFDCA to permit generic drug companies to gain approval of generic copies of innovator drugs (also called the “reference drug”) by referencing studies performed by the innovator, without having to expend the same considerable investment in time and resources as the innovator. Thus, generic drug companies are permitted to file what is referred to as an Abbreviated New Drug Application (“ANDA”) under 21 U.S.C. § 355(j). When filing an ANDA, generic drug companies are required to review the patent information that the FDA has published in the Orange Book for the reference drug and make a statutory certification (commonly called a “patent certification”) with respect to each listed patent.

36. The generic drug company may, *inter alia*, state that it does not seek FDA approval to market its generic drug product prior to patent expiration (a “Paragraph III certification”). *See* 21 U.S.C. § 355(j)(2)(A)(vii)(III). Alternatively, the generic drug company may seek FDA approval to market its generic drug product prior to patent expiration by alleging in its ANDA that one or more patents listed in the Orange Book is “invalid or will not be infringed” (commonly called a “Paragraph IV certification”). 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

37. The ‘483 Patent, identified in paragraph 1 of this Complaint, is listed in the Orange Book as a patent “with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.” 21 U.S.C. § 355(b)(1).

38. On information and belief, Natco filed ANDA No. 202-595 with the FDA seeking approval to market generic copies of Plaintiffs’ Tamiflu® 30 mg and 45 mg oseltamivir phosphate drug products prior to expiration of the ‘483 Patent.

39. On or about August 2, 2011, Dr. A.K.S. Bhujanga Rao, President-Technical of Natco Ltd., sent to Plaintiffs a letter purporting to be a notice of Natco's filing of an amended ANDA seeking to market a generic copy of Plaintiffs' Tamiflu® 30 mg and 45 mg oseltamivir phosphate drug products that allegedly contained the Paragraph IV certification required by 21 U.S.C. § 355(j)(2)(B)(ii) with respect to the '483 Patent listed in the Orange Book for Tamiflu® ("Amended Paragraph IV Notice").

40. In particular, Natco's Amended Paragraph IV Notice states that Natco is seeking FDA approval to market generic copies of the Tamiflu® 30 mg and 45 mg oseltamivir phosphate drug products prior to expiration of the '483 Patent listed in the Orange Book for Tamiflu®. Notwithstanding the United States Patent and Trademark Office's grant of patent protection, in its Amended Paragraph IV Notice, Natco asserts that the '483 Patent is invalid, unenforceable, and/or would not be infringed by its proposed generic products.

41. Natco's efforts to seek FDA approval to market generic copies of Plaintiffs' Tamiflu® 30 mg and 45 mg oseltamivir phosphate drugs product prior to expiration of the '483 Patent constitute acts of infringement pursuant to 21 U.S.C. § 271(e)(2) and, thus, create a justiciable controversy between the parties with respect to the subject matter of Natco's ANDA and the '483 Patent which has been challenged in Natco's Amended Paragraph IV Notice.

Count 1: Infringement under 35 U.S.C. § 271(e)(2)

42. Plaintiffs incorporate by reference paragraphs 1-41 of this Complaint as if fully set forth herein.

43. On information and belief, Natco Ltd. and Natco Inc., acting jointly, filed ANDA No. 202-595 in order to obtain approval to market Natco's generic copy of Plaintiffs' Tamiflu®

oseltamivir phosphate drug product in the United States before the expiration of the '483 Patent. On information and belief, Natco Ltd. and Natco Inc., acting jointly, also filed with the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (Section 505(j)(2)(A)(vii)(IV) of the FFDCA), a certification alleging that the claims of the '483 Patent are invalid and/or will not be infringed by their manufacture, use or sale of generic copies of Plaintiffs' Tamiflu® 30 mg and 45 mg oseltamivir phosphate drug products.

44. Under 35 U.S.C. § 271(e)(2)(A), Natco's submission to the FDA of ANDA No. 202-595 to obtain approval for the commercial manufacture, use, or sale of Natco's generic copies of Plaintiffs' Tamiflu® 30 mg and 45 mg oseltamivir phosphate drug products before the expiration date of the '483 Patent and any additional periods of exclusivity constitutes infringement of one or more claims of the '483 Patent, either literally or under the doctrine of equivalents.

45. Plaintiffs will be irreparably harmed by Natco's infringing activities unless such activities are enjoined by the Court as Plaintiffs do not have an adequate remedy at law. Plaintiffs are entitled to relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order by this Court that the effective date of any FDA approval of Natco's ANDA shall be no earlier than the expiration date of the '483 Patent and any additional periods of exclusivity.

Count 2: Infringement under 35 U.S.C. §§ 271(a)(b) and/or (c)

46. Plaintiffs incorporate by reference paragraphs 1-45 of this Complaint as if fully set forth herein.

47. On information and belief, Natco Ltd. and Natco Inc. acted in concert to jointly submit ANDA No. 202-595 in order to obtain approval to engage in the commercial manufacture, use or sale of generic copies of Plaintiffs' Tamiflu® 30 mg and 45 mg oseltamivir

phosphate drug products in the United States before the expiration date of the '483 Patent and any additional periods of exclusivity.

48. On information and belief, any commercial manufacture, use, offer for sale, sale, and/or importation of generic copies of Plaintiffs' Tamiflu® 30 mg and 45 mg oseltamivir phosphate drug products will infringe the '483 Patent under 35 U.S.C. §§ 271(a)(b) and/or (c).

49. Upon FDA approval of Natco's ANDA No. 202-595, Natco will directly infringe one or more claims of the '483 Patent, either literally or under the doctrine of equivalents, by making, using, offering to sell, selling, and/or importing Natco's generic copies of Plaintiffs' Tamiflu® 30 mg and 45 mg oseltamivir phosphate drug products in the United States, and by actively inducing and contributing to infringement by others under 35 U.S.C. §§ 271(b) and (c), unless this Court orders that the effective date of any FDA approval of Natco's ANDA shall be no earlier than the expiration date of the '483 Patent and any additional periods of exclusivity.

50. On information and belief, Natco's generic oseltamivir phosphate capsules, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '483 Patent, either literally or under the doctrine of equivalents.

51. On information and belief, the use of Natco's generic oseltamivir phosphate capsules constitutes a material part of at least one of the claims of the '483 Patent; Natco knows that its generic oseltamivir phosphate capsules are especially made or adapted for use in infringing at least one of the claims of the '483 Patent, either literally or under the doctrine of equivalents; and Natco's generic oseltamivir phosphate capsules are not staple articles of commerce or commodities of commerce suitable for substantial noninfringing use.

52. On information and belief, the offering to sell, sale, and/or importation of Natco's generic oseltamivir phosphate capsules would contributorily infringe at least one of the claims of the '483 Patent, either literally or under the doctrine of equivalents.

53. On information and belief, Natco had knowledge of the '483 Patent and knows or should know that it will aid and abet another's direct infringement of at least one of the claims of the '483 Patent, either literally or under the doctrine of equivalents.

54. On information and belief, the offering to sell, sale, and/or importation of Natco's generic oseltamivir phosphate capsules would actively induce infringement of at least one of the claims of the '483 Patent, either literally or under the doctrine of equivalents.

55. Plaintiffs will be substantially and irreparably harmed by Natco's infringing activities unless those activities are enjoined by this Court. Plaintiffs have no adequate remedy at law.

RELIEF SOUGHT

WHEREFORE, Plaintiffs respectfully request that this Court enter judgment in its favor as follows:

- A) a judgment that Natco has infringed the '483 Patent under 21 U.S.C. § 271(e)(2)(A) by submitting ANDA No. 202-595 with an Amended Paragraph IV certification seeking to market its generic copies of Tamiflu® oseltamivir phosphate drug products prior to the expiration date of said patent and any additional periods of exclusivity;
- B) a judgment and decree that the '483 Patent is valid and enforceable;
- C) an Order pursuant to 21 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of Natco's ANDA No. 202-595 be a date that is not earlier than the expiration date of the '483 Patent and any additional periods of exclusivity;

D) a judgment that Natco would infringe and induce infringement of the '483 Patent upon marketing its generic copies of Tamiflu® oseltamivir phosphate drug products prior to the expiration date of said patent and any additional periods of exclusivity;

E) a judgment declaring that if Natco, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf, engage in the commercial manufacture, use, offer for sale, and/or importation of Natco's generic copies of Tamiflu® oseltamivir phosphate drug products prior to the expiration date the '483 Patent and any additional periods of exclusivity, it will constitute acts of infringement of the '483 Patent under 35 U.S.C. §§ 271(a)(b) and/or (c);

F) a permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B) restraining and enjoining Natco and its officers, agents, servants and employees, and those persons in active concert or participation with any of them, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States of its generic copies of Tamiflu® oseltamivir phosphate drug products and any other drug products that infringe or induce or contribute to the infringement of the '483 Patent prior to the expiration date of the '483 Patent and any additional periods of exclusivity;

G) a judgment that this is an exceptional case and that Plaintiffs are entitled to an award of attorneys fees from Natco under 35 U.S.C. § 285; and

H) such other and further relief as the Court may deem just and proper.

Dated: August 29, 2011

CONNELL FOLEY LLP

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Roche Ltd. and Genentech, Inc.

CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 11.2

Pursuant to Local Civil Rule 11.2, I hereby certify that the matter in controversy is the subject of the following related litigation: *Gilead Sciences, Inc. et al. v. Natco Pharma Ltd. et al.*, Civil Action No. 11-1455 (SDW/MCA), initiated on March 15, 2011 in the United States District Court for the District of New Jersey; and *Gilead Sciences, Inc. et al. v. Natco Pharma Ltd. et al.*, Civil Action No. 11-cv-221, initiated on March 14, 2011 in the United States District Court for the District of Delaware. Other than those actions, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: August 29, 2011

s/Liza M. Walsh
Liza M. Walsh

CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 201.1

Pursuant to Local Civil Rule 201.1, I hereby certify that the matter in controversy is not subject to compulsory arbitration in that Plaintiffs seek, *inter alia*, declaratory and injunctive relief.

Dated: August 29, 2011

s/Liza M. Walsh
Liza M. Walsh

EXHIBIT A



US005763483A

United States Patent [19]

Bischofberger et al.

[11] Patent Number: 5,763,483
 [45] Date of Patent: Jun. 9, 1998

[54] CARBOCYCLIC COMPOUNDS

[75] Inventors: **Norbert W. Bischofberger; Choung U. Kim**, both of San Carlos; **Willard Lew**, San Mateo; **Hongtao Liu; Matthew A. Williams**, both of Foster City, all of Calif.

[73] Assignee: **Gilead Sciences, Inc.**, Foster City, Calif.

[21] Appl. No.: 774,345

[22] Filed: Dec. 27, 1996

Related U.S. Application Data

[60] Provisional application No. 60/009,306 Dec. 29, 1995.

[51] Int. Cl.⁶ A61K 31/21

[52] U.S. Cl. 514/529; 514/563; 548/190; 548/217; 548/250; 548/953; 548/961; 549/33; 549/331; 549/399; 549/434; 549/546; 558/430; 558/431; 560/125

[58] Field of Search 514/529, 563; 562/507; 560/125

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(List continued on next page.)

Primary Examiner—Donald G. Daus

Attorney, Agent, or Firm—Mark L. Bosse

[57] ABSTRACT

Novel carbocyclic compounds are described. The compounds generally comprise an acidic group, a basic group, a substituted amino or N-acyl and a group having an optionally hydroxylated alkane moiety. Pharmaceutical compositions comprising the inhibitors of the invention are also described. Methods of inhibiting neuraminidase in samples suspected of containing neuraminidase are also described. Antigenic materials, polymers, antibodies, conjugates of the compounds of the invention with labels, and assay methods for detecting neuraminidase activity are also described.

7 Claims, No Drawings

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W_1 is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

W_2 is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W_3 is W_4 or W_5 ;

W_4 is R_5 or $—C(O)R_5$, $—C(O)W_5$, $—SO_2R_5$, or $—SO_2W_5$;

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

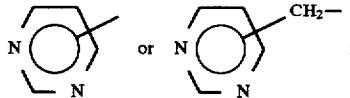
W_6 is $—R_5$, $—W_5$, $—R_{5a}W_5$, $—C(O)OR_{6a}$, $—C(O)R_{6c}$, $—C(O)NR_{6b}R_{6b}$, $—C(NR_{6b})NR_{6b}R_{6b}$, $—C(S)NR_{6b}R_{6b}$, or $—C(O)R_2$;

X_1 is a bond, $—O—$, $—NR_5—$, $—N(OR_5)—$, $—N(NR_5R_5)—$, $—S—$, $—SO—$, or $—SO_2—$; and

each m_1 is independently an integer from 0 to 2; provided, however, that compounds are excluded wherein:

(a) E_1 is $—CO_2H$, $—P(O)(OH)_2$, $—NO_2$, $—SO_2H$, $—SO_3H$, tetrazolyl, $—CH_2CHO$, $—CHO$, or $—CH(CHO)_2$;

(b) G_1 is $—CN$, NR_{20} , N_3 , $—O(R_{20})$, SR_{20} , guanidino, $—N(R_{20})(OR_{20})$, $—N(R_{20})—O$, NHR_{20} , $—N(H)(R_{20})N(R_{20})_2$.



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(c) T_1 is $—NHR_{20}$ or $—NO_2$;

(d) R_{20} is H; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; an allyl group or an unsubstituted aryl group or an aryl substituted by a halogen, an OH group, an NO_2 group, an NH_2 group or a $COOH$ group;

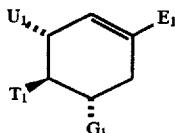
(e) J_1 is H;

(f) U_1 is $—CH_2YR_{20a}$, $—CH(YR_{20a})CH_2YR_{20a}$ or $—(CH(YR_{20a})CH(YR_{20a}))CH_2YR_{20a}$;

(g) R_{20a} is H or acyl having 1 to 4 carbon atoms; and Y is O or S, 0 to 2 YR_{20a} are H, and successive Y moieties in a U_1 group are the same or different, and the pharmaceutically acceptable salts thereof;

and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

Another embodiment of the invention is directed to compounds of the formula:



wherein:

E_1 is $—CO_2R_1$;

G_1 is $—NH_2$, or $—N(H)(C(N(H))(NH_2))$;

T_1 is $—N(H)(C(O)CH_3)$;

U_1 is $—OR_{60}$;

R_1 is H or an alkyl of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms; and

R_{60} is a branched alkyl of 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms;

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and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

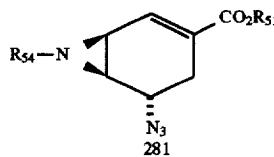
In another embodiment of the invention a compound or composition of the invention is provided that further comprises a pharmaceutically-acceptable carrier.

In another embodiment of the invention the activity of neuraminidase is inhibited by a method comprising the step of treating a sample suspected of containing neuraminidase with a compound or composition of the invention.

In a particular embodiment of the invention, influenza is treated by administering to an animal infected by or at risk to infection by influenza virus a therapeutically effective amount of a compound having formula (I) or (II) as set forth above.

In other embodiments, novel methods for synthesis of the compounds of this invention are provided.

In one method embodiment, a method is provided for using a compound of the formula:

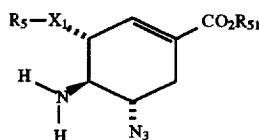


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wherein the method comprises treating compound 281 with a compound of the formula:



to form a compound of the formula:



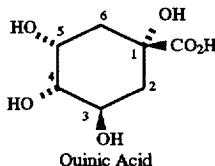
wherein:

X_1 and R_5 are as described above;

R_{51} is an acid stable protecting group for a carboxylic acid; and

R_{54} aziridine activating group.

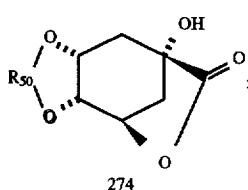
In another method embodiment, a method is provided for using a compound of the formula:



wherein the method comprises treating Quinic acid with a geminal dialkoxyalkane or geminal dialkoxy cycloalkane and acid to form a compound of the formula:

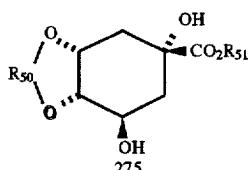
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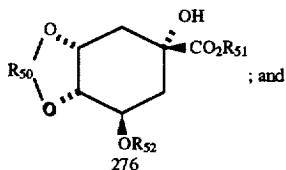
274

treating compound 274 with a metal alkoxide and an alkanol to form a compound of the formula:



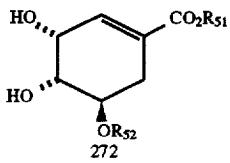
275

treating compound 275 with a sulfonic acid halide and an amine to form a compound of the formula:



276

treating compound 276 with a dehydrating agent followed by an acid and an alkanol to form a compound of the formula:



272

wherein:

R₅₀ is a 1,2 diol protecting group;
R₅₁ is an acid stable carboxylic acid protecting group;
and
R₅₂ is a hydroxy activating group.

DETAILED DESCRIPTION

Compositions of the Invention

The compounds of this invention exclude compounds heretofore known, although in other embodiments it is within the invention to use as antiviral compounds those known compounds which heretofore were produced as intermediates. For purposes of the United States application, the compounds or compositions herein exclude compounds that are anticipated under 35 USC 102 or that are obvious thereover under 35 USC 103. Accordingly, the claims herein shall be construed as excluding the compounds specifically described in WO 91/16320 and in WO 92/06691, both of which are expressly incorporated herein by reference. In addition, the compound and composition claims shall be construed to exclude prior art compounds set forth in the background sections of the aforementioned International publication and the present application.

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In applicants' view, the compounds of the art suffer from numerous deficiencies, in particular ephemeral biological half life and unsatisfactory limitations in the manner of dosing brought on by the biological instability of the compounds. Accordingly, it is part of the invention herein to select from the '320 and '691 publications compounds that otherwise are identical to those taught therein except that (a) the enol ring structure of formula Ia of the '320 application is selected, (b) group "A" in the '320 application is selected to be carbon, so that the intraring heteroatom is dispensed with, and (c) the polyol or in vivo-unstable protected polyol structure, found at R⁵ of the '320 and '691 applications, is dispensed with, so that in the '320 application, R⁵ is selected to denote "—CH₂YR⁶", "—CHYR⁶CH₂YR⁶" or "—CHYR⁶CHYR⁶CH₂YR⁶" but no YR⁶ is OH, or in vivo-hydrolyzable OPR where PR is a protecting group as described in the '320 or '691 applications that is removed in the conditions found in the human gastrointestinal tract. In regard to the noted stable OPR compounds of the '320 or '691 applications, it is part of the invention herein to administer to a subject for the treatment or prophylaxis of influenza infection compounds in which YR⁶ optionally is stable OPR and R⁵ does not contain free hydroxyl, in particular compounds in which PR is other than acyl having 1-4 carbon atoms.

In one embodiment, the compounds herein exclude those in which

- (a) E₁ is —CO₂H, —P(O)(OH)₂, —NO₂, —SO₂H, —SO₃H, tetrazolyl, —CH₂CHO, —CHO, or —CH(CHO)₂;
- (b) G₁ is —CN, N₃, —NHR₂₀, NR₂₀, —OR₂₀, guanidino, SR₂₀, —N(R₂₀)₂O, —N(R₂₀)(OR₂₀), —N(H)(R₂₀)N(R₂₀)₂, unsubstituted pyrimidinyl, or unsubstituted (pyrimidinyl)methyl;
- (c) T₁ is —NHR₂₀, —NO₂; and R₂₀ is H; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; an allyl group or an unsubstituted aryl group or an aryl substituted by a halogen, an OH group, an NO₂ group, an NH₂ group or a COOH group;
- (d) each J₁ is H; and
- (e) X₁ is a bond, —CH₂— or —CH₂CH₂—;

in which case W₆ is not H, W₇ or —CH₂W₇, wherein W₇ is H, —OR_{6a}, —OR₁, —N(R₁)₂, —N(R₁)(R_{6b}), —N(R_{6b})₂, —SR₁, or —SR_{6a}.

In another embodiment, the compounds of this invention include those in which group U₁ is not bonded directly to the cyclohexene nucleus by a carbon atom. In a further embodiment, U₁ is not substituted with hydroxyl or hydroxyester, in particular U₁ is not polyhydroxylalkane, especially —CH(OH)CH(OH)CH₂CH₂OH. In a further embodiment, U₁ is a branched chain group R₅ as described below or a carbocycle which is substituted with at least one group R₅.

Whenever a compound of this invention is substituted with more than one of the same designated group, e.g., "R₁" or "R_{6a}", then it will be understood that the groups may be the same or different, i.e., each group is independently selected.

"Heterocycle" as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York,

1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem. Soc.", 82:5566 (1960), each of which is incorporated herein by reference.

Examples of heterocycles include by way of example and not limitation pyridyl, thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thieryl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thieryl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl.

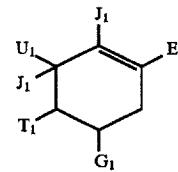
By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrrolidine, 3-pyrrolidine, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetidyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

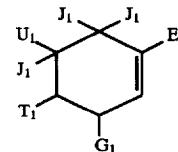
"Alkyl" as used herein, unless stated to the contrary, is C_1-C_{12} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, $—CH_3$), ethyl (Et, $—CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $—CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $—CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $—CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $—CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $—CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $—C(CH_3)_3$), 1-pentyl (n-pentyl, $—CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($—CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($—CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($—C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($—CH(CH_3)CH(CH_3)CH_2CH_3$), 3-methyl-1-butyl ($—CH_2CH_2CH(CH_3)_2$).

2-methyl-1-butyl ($—CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($—CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($—CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($—CH(CH_2CH_3)CH_2CH_2CH_3$), 2-methyl-2-pentyl ($—C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($—CH(CH_3)CH_2CH(CH_3)_2$), 4-methyl-2-pentyl ($—CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($—C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($—CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($—C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($—CH(CH_3)C(CH_3)_3$). Examples of alkyl groups appear in Table 2 as groups 2-5, 7, 9, and 100-399.

The compositions of the invention comprise compounds of either formula:



or



In the typical embodiment, the compounds of Formula I are chosen. Each J_1 is independently H, F or Cl, typically H or F, more typically H. E_1 is $—(CR_1R_1)_{m_1}W_1$.

Typically, R_1 is H or alkyl of 1 to 12 carbon atoms, usually H or an alkyl of 1 to 4 or 5 to 10 carbon atoms, still more typically, H or an alkyl of 1 to 3 carbon atoms selected from methyl, ethyl, n-propyl, and i-propyl. Most typically R_1 is H. m_1 is an integer of 0 to 2, typically 0 or 1, most typically 0.

m_2 is an integer of 0 to 1.

m_3 is an integer of 1 to 3.

W_1 is a group comprising an acidic hydrogen or a protected acidic group, which, within the context of the invention, means a group having a hydrogen atom that can be removed by a base yielding an anion or its corresponding salt or solvate. The general principles of acidity and basicity of organic materials are well understood and are to be understood as defining W_1 . They will not be detailed here. However, a description appears in Streitwieser, A.; and Heathcock, C. H.; "Introduction to Organic Chemistry, Second Edition" (Macmillan, New York, 1981), pages 60-64. Generally, acidic groups of the invention have pK values less than that of water, usually less than $pK=10$, typically less than $pK=8$, and frequently less than $pK=6$. They include tetrazoles and the acids of carbon, sulfur, phosphorous and nitrogen, typically the carboxylic, sulfuric, sulfonic sulfonic, phosphoric and phosphonic acids, together with the R_{6a} amides and R_{6b} esters of those acids (R_{6a} and R_{6b} are defined below). Exemplary W_1 are $—CO_2H$, $—CO_2R_{6a}$, $—OSO_3H$, $—SO_2H$, $—OPO_3H_2$,

$—PO_3(R_{6a})_2$, $—PO_3H_2$, $—PO_3(H)(R_{6a})$, and $—OPO_3(R_{6a})_2$. W_1 typically is E_1 , and E_1 typically is $—CO_2H$, $—CO_2R_{6a}$, $—CO_2R_4$ or CO_2R_1 , and most typically is CO_2R_{14} wherein R_{14} is normal or terminally secondary C_1-C_6 alkyl.

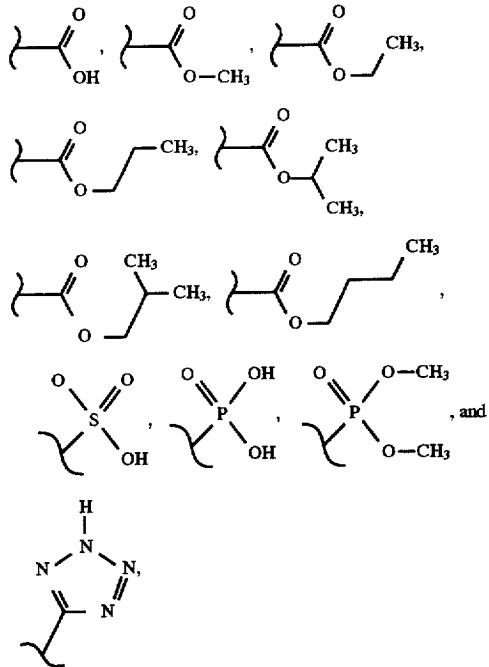
W_1 may also be a protected acidic group, which, within the context of the invention means an acidic group as described above that has been protected by one of the groups commonly used in the art for such groups and are described

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below under R_{6a} . More typically, protected W_1 is $-\text{CO}_2\text{R}_1$, $-\text{SO}_3\text{R}_1$, $-\text{S}(\text{O})\text{OR}_1$, $-\text{P}(\text{O})(\text{OR}_1)_2$, $-\text{C}(\text{O})\text{NHSO}_2\text{R}_4$, or $-\text{SO}_2\text{NHC(O)}-\text{R}_4$, wherein R_1 is defined above.

Most typically, E_1 is selected from $-\text{C}(\text{O})\text{O}(\text{CH}_2)_b\text{CH}(\text{CH}_2)_c\text{CH}_3$ where $b=0$ to 4, $c=0$ to 4, and $b+c=1$ to 4, or from the group of



Exemplary E_1 groups are listed in Tables 3a through 3b. G_1 is N_3 , $-\text{CN}$, $-\text{OH}$, $-\text{NO}_2$, OR_{6a} or $-(\text{CR}_1\text{R}_1)_{m1}\text{W}_2$, wherein R_1 and $m1$ are defined above. Ordinarily, G_1 is $-(\text{CR}_1\text{R}_1)_{m1}\text{W}_2$.

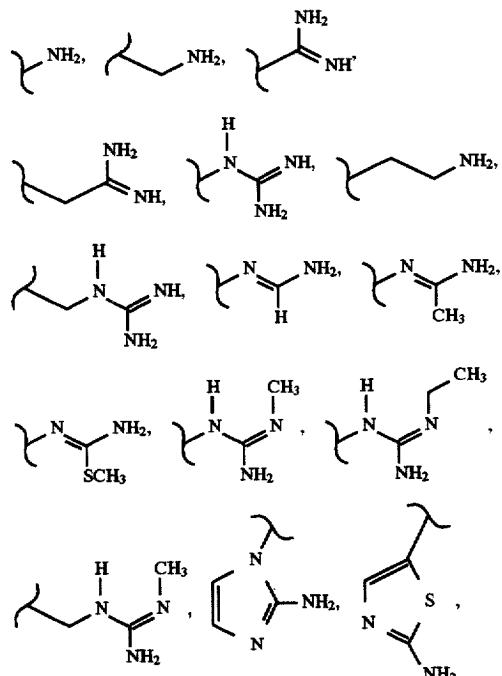
W_2 is a group comprising a basic heteroatom or a protected basic heteroatom. W_2 generally comprises a basic heteroatom, which, within the context of the invention means an atom other than carbon which is capable of protonation, typically by an acidic hydrogen having an acidity in the range described above for W_1 . The basic principles of basicity are described in Streitwieser and Heathcock (op. cit.) and provide meaning for the term basic heteroatom as will be understood by those ordinarily skilled in the art. Generally, the basic heteroatoms employed in the compounds of the invention have pK values for the corresponding protonated form that are in the range of values described above for W_1 . Basic heteroatoms include the heteroatoms common in organic compounds which have an un-shared, non-bonding, n-type, or the like, electron pair. By way of example and not limitation, typical basic heteroatoms include the oxygen, nitrogen, and sulfur atoms of groups such as alcohols, amines, amidines, guanidines, sulfides, and the like, frequently, amines, amidines and guanidines. Ordinarily, W_2 is amino or an amino alkyl (generally lower alkyl) group such as aminomethyl, aminoethyl or aminopropyl; an amidinyl, or an amidinoalkyl group such as amidinomethyl, amidinoethyl, or amidinopropyl; or guanidinyl, or a guanidinoalkyl group such as guanidinomethyl, guanidinoethyl, or guanidinopropyl (in each instance wherein the alkyl group serves to bridge the basic substituent to the carbocyclic ring). More typically, W_2 is amino, amidino, guanidino, heterocycle, heterocycle substituted with 1 or 2 amino or guanidino groups (usually 1), or an alkyl of 2 to 3 carbon atoms substituted with amino or

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guanidino, or such alkyl substituted with an amino and a second group selected from the group consisting of hydroxy and amino. The heterocycles useful as W_2 include typically N or S-containing 5 or 6 membered rings, wherein the ring contains 1 or 2 heteroatoms. Such heterocycles generally are substituted at ring carbon atoms. They may be saturated or unsaturated and may be linked to the core cyclohexene by lower alkyl ($m1=1$ or 2) or by $-\text{NR}_1-$. Still more typically, W_2 is $-\text{NHR}_1$, $-\text{C}(\text{NH})(\text{NH}_2)$, $-\text{NR}_1-\text{C}(\text{NR}_1)(\text{NR}_1\text{R}_3)$, $-\text{NH}-\text{C}(\text{NH})(\text{NHR}_3)$, $-\text{NH}-\text{C}(\text{NH})(\text{NHR}_1)$, $-\text{NH}-\text{C}(\text{NH})(\text{NH}_2)$, $-\text{CH}(\text{CH}_2\text{NHR}_1)(\text{CH}_2\text{OH})$, $-\text{CH}(\text{CH}_2\text{NHR}_1)(\text{CH}_2\text{NHR}_1)$, $-\text{CH}(\text{NHR}_1)-(\text{CR}_1\text{R}_1)_{m2}-\text{CH}(\text{NHR}_1)\text{R}_1$, $-\text{CH}(\text{OH})-(\text{CR}_1\text{R}_1)_{m2}-\text{CH}(\text{NHR}_1)\text{R}_1$, or $-\text{CH}(\text{NHR}_1)-(\text{CR}_1\text{R}_1)_{m2}-\text{CH}(\text{OH})\text{R}_1$, $-(\text{CR}_1\text{R}_1)_{m2}-\text{S}-\text{C}(\text{NH})(\text{NH}_2)$, $-\text{N}=\text{C}(\text{NHR}_1)(\text{R}_3)$, $-\text{N}=\text{C}(\text{SR}_1)\text{N}(\text{R}_1)_2$, $-\text{N}(\text{R}_1)\text{C}(\text{NH})(\text{N}(\text{R}_1)\text{C}=\text{N}$, or $-\text{N}=\text{C}(\text{NHR}_1)(\text{R}_1)$; wherein each $m2$ is ordinarily 0, and ordinarily R_1 is H and R_3 is $\text{C}(\text{O})\text{N}(\text{R}_1)_2$.

W_2 optionally is a protected basic heteroatom which within the context of the invention means a basic heteroatom as described above that has, been protected by R_{6b} such as one of the groups common in the art. Such groups are described in detail in Greene (op. cit.) as set forth below. Such groups include by way of example and not limitation, amides, carbamates, amino acetals, imines, enamines, N-alkyl or N-aryl phosphinyls, N-alkyl or N-aryl sulfenyls or sulfonyls, N-alkyl or N-aryl silyls, thioethers, thioesters, disulfides, sulfenyls, and the like. In some embodiments, the protecting group R_{6b} will be cleavable under physiological conditions, typically it will be cleavable in vivo where, for example, the basic heteroatom forms an amide with an organic acid or an amino acid such as a naturally occurring amino acid or a polypeptide as described below for the R_{6a} group.

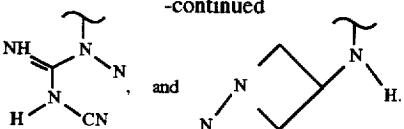
Typically G_1 is selected from the group consisting of:



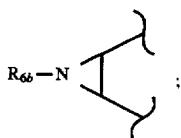
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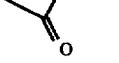
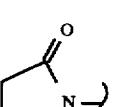
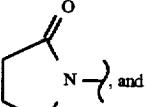
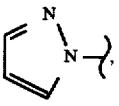
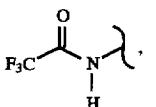
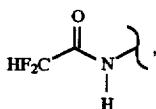
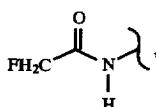
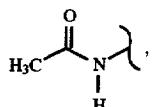
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Further exemplary G_1 groups are listed in Tables 4a-4c. T_1 is $-NR_1W_3$ or heterocycle, or is taken together with U_1 or G_1 to form a group having the structure



where R_{6b} is defined below, and R_1 and W_3 are defined above. Generally T_1 is selected from the group consisting of:



Exemplary T_1 groups are listed in Tables 5a-5d.

W_3 is W_4 or W_5 , wherein W_4 is R_1 or $-C(O)R_5$, $-C(O)W_5$, $-SO_2R_5$, or $-SO_2W_5$. Typically, W_3 is $-C(O)R_5$ or W_5 .

R_2 is R_3 or R_4 as defined below, with the proviso that each R_4 is independently substituted with 0 to 3 R_3 groups;

R_3 is F, Cl, Br, I, $-CN$, N_3 , NO_2 , $-OR_{6a}$, $-OR_1$, $-N(R_1)_2$, $-N(R_1)(R_{6b})$, $-N(R_{6b})_2$, $-SR_1$, $-SR_{6a}$, $-C(O)OR_1$, $-C(O)R_{6c}$, $-C(O)OR_{6a}$, $-OC(O)R_1$, $-NR_1C(O)R_1$, $-N(R_{6b})C(O)R_1$, $-C(O)N(R_1)_2$, $-C(O)N(R_1)(R_{6b})_2$.

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$(R_{6b})(R_1)$, $-C(O)N(R_{6b})_2$, $-C(NR_1)(N(R_1)_2)$, $-C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_1)C(N(R_1))(N(R_1)_2)$, $-N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1)(R_{6b}))$, $=O$, $=S$, $=N(R_{6b})$ or $=N(R_1)$. Typical R_3 groups comprising R_{6b} include $-C(O)N(R_{6b})_2$, $-C(O)N(R_{6b})(R_1)$, $-C(S)N(R_{6b})_2$, or $-C(S)N(R_{6b})(R_1)$. Typically R_3 is F, Cl, $-CN$, N_3 , $-OR_1$, $-N(R_1)_2$, $-SR_1$, $-C(O)OR_1$, $-OC(O)R_1$, or $=O$. More typically, R_3 is F, $-OR_1$, $-N(R_1)_2$, or $=O$. In the context of the present application, " $=O$ " denotes a double bonded oxygen atom (oxo), and " $=S$ " $=N(R_{6b})$ and " $=N(R_1)$ " denote the sulfur and nitrogen analogs.

R_4 is alkyl of 1 to 12 carbon atoms, and alkynyl or alkenyl of 2 to 12 carbon atoms. R_4 ordinarily is alkyl (as defined above). When R_4 is alkenyl it is typically ethenyl ($-CH=CH_2$), 1-prop-1-enyl ($-CH=CHCH_3$), 1-prop-2-enyl ($-CH_2CH=CH_2$), 2-prop-1-enyl ($-C(CH_2)CH_3$), 1-but-1-enyl ($-CH=CHCH_2CH_3$), 1-but-2-enyl ($-CH_2CH=CHCH_3$), 1-but-3-enyl ($-CH_2CH_2CH=CH_2$), 2-methyl-1-prop-1-enyl ($-CH=C(CH_3)_2$), 2-methyl-1-prop-2-enyl ($-CH_2C(CH_3)=CH_2$), 2-but-1-enyl ($-C(CH_2)CH_2CH_3$), 2-but-2-enyl ($-C(CH_3)=CHCH_2CH_3$), 2-but-3-enyl ($-CH(CH_3)CH=CH_2$), 1-pent-1-enyl ($-C=CHCH_2CH_2CH_3$), 1-pent-2-enyl ($-CHCH=CHCH_2CH_3$), 1-pent-3-enyl ($-CH_2CH_2CH=CHCH_3$), 1-pent-4-enyl ($-CH_2CH_2CH_2CH=CH_2$), 2-pent-1-enyl ($-C(CH_2)=CHCH_2CH_3$), 2-pent-2-enyl ($-C(CH_3)=CH_2CH_2CH_3$), 2-pent-3-enyl ($-CH(CH_3)CH=CHCH_3$), 2-pent-4-enyl ($-CH(CH_3)CH_2CH=CH_2$) or 3-methyl-1-but-2-enyl ($-CH_2CH=C(CH_3)_2$). More typically, R_4 alkenyl groups are of 2, 3 or 4 carbon atoms. When R_4 is alkynyl it is typically ethynyl ($-CCH$), 1-prop-1-ynyl ($-CCCH_3$), 1-prop-2-ynyl ($-CH_2CCH$), 1-but-1-ynyl ($-CCCH_2CH_3$), 1-but-2-ynyl ($-CH_2CCCH_3$), 1-but-3-ynyl ($-CH_2CH_2CCH$), 2-but-3-ynyl ($CH(CH_3)CCH$), 1-pent-1-ynyl ($-CCCH_2CH_2CH_3$), 1-pent-2-ynyl ($-CH_2CCCH_2CH_3$), 1-pent-3-ynyl ($-CH_2CH_2CCCH_3$) or 1-pent-4-ynyl ($-CH_2CH_2CH_2CCH$). More typically, R_4 alkynyl groups are of 2, 3 or 4 carbon atoms.

R_5 is R_4 , as defined above, or R_4 substituted with 0 to 3 R_3 groups. Typically R_5 is an alkyl of 1 to 4 carbon atoms substituted with 0 to 3 fluorine atoms.

R_{5a} is alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms which is substituted with 0-3 R_3 groups.

R_{10} is alkyl, alkenyl, alkynyl of 1 to 12 carbon atoms substituted with 0 to 3 R_2 .

R_{11} is independently H or R_{10} .

R_{12} is a cycloalkyl of 3 to 10 carbon atoms, or cycloalkenyl of 4 to 10 carbon atoms.

R_{14} is normal or terminally secondary C_1-C_6 alkyl.

W_5 is a carbocycle or heterocycle, with the proviso that each W_5 is independently substituted with 0 to 3 R_2 groups.

W_5 carbocycles and T_1 and W_5 heterocycles are stable chemical structures. Such structures are isolatable in measurable yield, with measurable purity, from reaction mixtures at temperatures from -78° C. to 200° C. Each W_5 is independently substituted with 0 to 3 R_2 groups. Typically, T_1 and W_5 are a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. More typically, T_1 or W_5 has 3 to 10 ring atoms, still more typically, 3 to 7 ring atoms, and ordinarily 3 to 6 ring atoms. The T_1 and W_5 rings are saturated when containing 3 ring

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atoms, saturated or monounsaturated when containing 4 ring atoms, saturated, or mono- or diunsaturated when containing 5 ring atoms, and saturated, mono- or diunsaturated, or aromatic when containing 6 ring atoms.

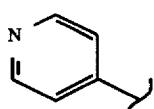
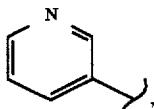
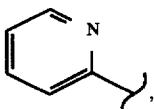
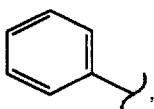
When W_5 is carbocyclic, it is typically a 3 to 7 carbon monocycle or a 7 to 12 carbon atom bicyclic. More typically, W_5 monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. W_5 bicyclic carbocycles have 7 to 12 ring atoms arranged as a bicyclo [4.5], [5.5], [5.6] or [6.6] system, still more typically, 9 or 10 ring atoms arranged as a bicyclo [5.6] or [6.6] system. Examples include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

A T_1 or W_5 heterocycle is typically a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicyclic having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). More typically, T_1 and W_5 heterocyclic monocycles have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S), still more typically, 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). T_1 and W_5 heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4.5], [5.5], [5.6], or [6.6] system, still more typically, 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 heteroatoms selected from N and S) arranged as a bicyclo [5.6] or [6.6] system.

Typically T_1 and W_5 heterocycles are selected from pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thifuranyl, thienyl, or pyrrolyl.

More typically, the heterocycle of T_1 and W_5 is bonded through a carbon atom or nitrogen atom thereof. Still more typically T_1 heterocycles are bonded by a stable covalent bond through a nitrogen atom thereof to the cyclohexene ring of the compositions of the invention and W_5 heterocycles are bonded by a stable covalent bond through a carbon or nitrogen atom thereof to the cyclohexene ring of the compositions of the invention. Stable covalent bonds are chemically stable structures as described above.

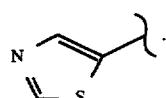
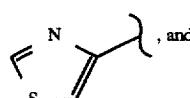
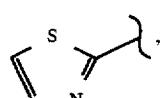
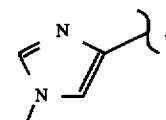
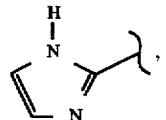
W_5 optionally is selected from the group consisting of:



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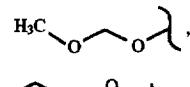
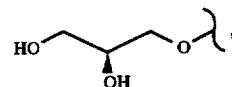
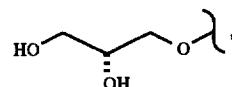
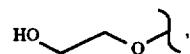
U_1 is H or $-X_1W_6$, but typically the latter.

X_1 is a bond, $-CR_1R_1-$, $-(CR_1R_1)_2-$, $-O-$, $-NR_1-$, $N(OR_1)-$, $-N(NR_1R_1)-$, $-S-$, $-SO-$, or $-SO_2-$. Ordinarily X_1 is $-O-$, $-NH-$, $-S-$, $-SO-$, or $-SO_2-$.

W_6 is $-R_5$, $-W_5$, $-R_{5a}W_5$, $-C(O)OR_{6a}$, $-C(O)R_{6c}$, $-C(O)NR_{6b}R_{6b}$, $-C(NR_{6b})NR_{6b}R_{6b}$, $-C(S)NR_{6b}R_{6b}$, or $-C(O)R_2$; in some embodiments, W_6 is R_1 , $-C(O)-R_1$, $-CHR_1W_7$, $-CH(R_1)_aW_7$, $-CH(W_7)_2$, (where a is 0 or 1, but is 0 when W_7 is divalent) or $-C(O)W_7$. In some embodiments, W_6 is $-CHR_1W_7$, or $-C(O)W_7$, or W_6 is $-(CH_2)_{m_1}CH((CH_2)_{m_3}R_3)_2$, $-(CH_2)_{m_1}C((CH_2)_{m_3}R_3)_3$; $-(CH_2)_{m_1}CH((CH_2)_{m_3}R_3)_{m_3}R_5aW_5$; $-(CH_2)_{m_1}C((CH_2)_{m_3}R_3)_2(CH_2)_{m_3}R_5aW_5$; $-(CH_2)_{m_1}C((CH_2)_{m_3}R_3)(CH_2)_{m_3}R_5aW_5$; or $-(CH_2)_{m_1}C((CH_2)_{m_3}R_3)_2(CH_2)_{m_3}R_5aW_5$; and wherein m_3 is an integer from 1 to 3.

W_7 is R_3 or R_5 , but typically is alkyl of 1 to 12 carbons substituted with 0 to 3 R_3 groups, the latter typically selected from the group consisting of $-NR_1(R_{6b})$, $-N(R_{6b})_2$, $-OR_{6a}$, or SR_{6a} . More typically, W_7 is $-OR_1$ or an alkyl of 3 to 12 carbon atoms substituted with OR_1 .

In general, U_1 is R_1O- , $-OCHR_1W_7$.



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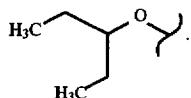
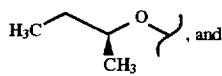
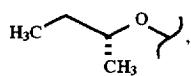
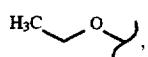
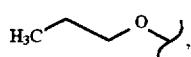
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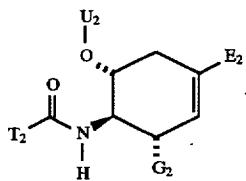
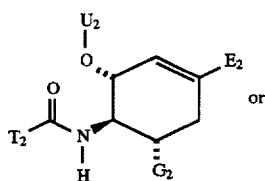
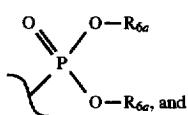
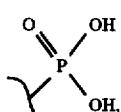
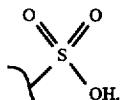
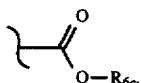
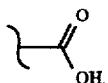
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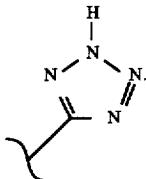
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Exemplary U_1 groups are listed in Tables 2a-2h.

An embodiment of the invention comprises a compound of the formula:

wherein E_2 is E_1 , but is typically selected from the group consisting of:**16**

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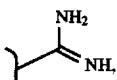
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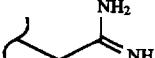
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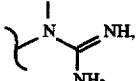
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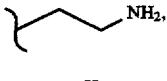
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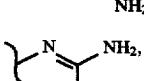
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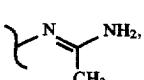
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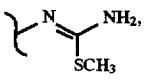
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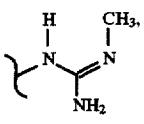
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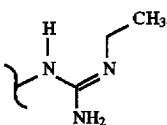
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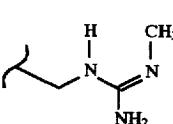
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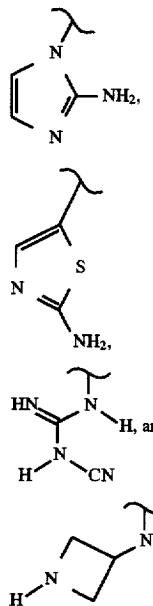
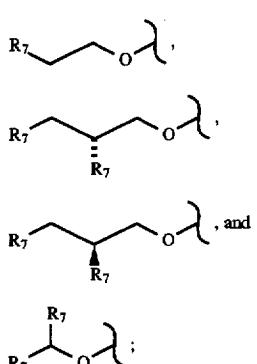
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and wherein G_2 is G_1 , but is typically selected from the group consisting of:

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-continued

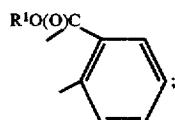
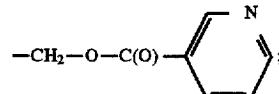
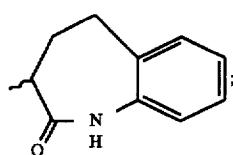
25 and wherein T_2 is R_4 or R_5 . Generally, T_2 is alkyl of 1 to 2 carbon atoms substituted with 0 to 3 fluorine atoms. U_2 is one of:45 wherein R_7 is H, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, $-\text{OAc}$ ($-\text{O}-\text{C}(\text{C})\text{CH}_3$), $-\text{OH}$, $-\text{NH}_2$, or $-\text{SH}$.Groups R_{6a} and R_{6b} are not critical functionalities and may vary widely.50 R_{6a} is H or an ether- or ester-forming group. Particularly of interest are ether- or ester-forming groups that are capable of functioning as protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are dealt with as amides, discussed under R_{6c} below. R_{6c} is capable of 55 protecting hydroxyl or thio groups such that hydrolysis from the parental molecule yields hydroxyl or thio.In its ester-forming role, R_{6a} typically is bound to any acidic group such as, by way of example and not limitation, a $-\text{CO}_2\text{H}$ or $-\text{C}(\text{S})\text{OH}$ group, thereby resulting in 60 $-\text{CO}_2\text{R}_{6a}$. R_{6a} for example is deduced from the ester groups of WO 95/07920. R_{6a} is not critical because its ordinary role is to serve as an intermediate for the active drug product or parental molecule of this invention. It is removed either in vitro or in vivo, so it is not even necessary 65 in the first instance that the resulting alcohol be physiologically acceptable.

18

Examples of R_{6a} include

5 $C_3\text{--}C_{12}$ heterocycle (described above) or aryl, either polycyclic or monocyclic. Examples include phenyl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-pyrimidinyl.

10 $C_3\text{--}C_{12}$ aryl substituted with halo, R_1 , $R_1\text{--O--C}_1\text{--C}_{12}$ alkylene, $C_1\text{--}C_{12}$ alkoxy, CN, NO_2 , OH, carboxy, carboxyester, thiol, thioester, $C_1\text{--}C_{12}$ haloalkyl (1-6 halogen atoms), $C_2\text{--}C_{12}$ alkenyl or $C_2\text{--}C_{12}$ alkynyl [including 2-, 3- and 4-alkoxyphenyl ($C_1\text{--}C_{12}$ alkyl), 2-, 3- and 4-methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2-, 3-, 2.4-, 2.5-, 2.6-, 3.4- and 3.5-diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2.3-, 2.4-, 2.5-, 2.6-, 3.4- and 3.5-dimethylphenyl, 2.3-, 2.4-, 2.5-, 2.6-, 3.4- and 3.5-bis carboxyethylphenyl, 2.3-, 2.4-, 2.5-, 2.6-, 3.4- and 3.5-dimethoxyphenyl, 2.3-, 2.4-, 2.5-, 2.6-, 3.4- and 3.5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms), $C_1\text{--}C_{12}$ alkyl including 4-trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms), $C_1\text{--}C_{12}$ alkyl including 4-trifluoromethylbenzyl and 2-, 3- and 4-trichloromethylbenzyl and 2-, 3- and 4-trichloromethylphenyl, 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 1-ethylpiperazinyl, benzyl, alkyl-salicylphenyl ($C_1\text{--}C_4$ alkyl, including 2-, 3- and 4-ethylsalicylphenyl), 2-, 3- and 4-acetylphenyl, 1,8-dihydroxynaphthyl ($-\text{O--C}_{10}\text{H}_6\text{--OH}$) and aryloxyethyl [$C_6\text{--}C_9$ aryl (including phenoxyethyl)], 2,2-dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, $-\text{C}_6\text{H}_4\text{CH}_2\text{--N}(\text{CH}_3)_2$, trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C_{1-4} alkyl);



$C_4\text{--}C_8$ esters of 2-carboxyphenyl; and $C_1\text{--}C_4$ alkylene- $C_3\text{--}C_6$ aryl (including benzyl, $-\text{CH}_2\text{-pyrrolyl}$, $-\text{CH}_2\text{-thienyl}$, $-\text{CH}_2\text{-imidazolyl}$, $-\text{CH}_2\text{-oxazolyl}$, $-\text{CH}_2\text{-isoxazolyl}$, $-\text{CH}_2\text{-thiazolyl}$, $-\text{CH}_2\text{-isothiazolyl}$, $-\text{CH}_2\text{-pyrazolyl}$, $-\text{CH}_2\text{-pyridinyl}$ and $-\text{CH}_2\text{-pyrimidinyl}$) substituted in the aryl moiety by 3 to 5

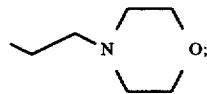
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halogen atoms or 1 to 2 atoms or groups selected from halogen, C₁–C₁₂ alkoxy (including methoxy and ethoxy), cyano, nitro, OH, C₁–C₁₂ haloalkyl (1 to 6 halogen atoms; including —CH₂CCl₃), C₁–C₁₂ alkyl (including methyl and ethyl), C₂–C₁₂ alkenyl or C₂–C₁₂ alkynyl;

alkoxy ethyl [C₁–C₆ alkyl including —CH₂—CH₂—O—CH₃ (methoxy ethyl)];

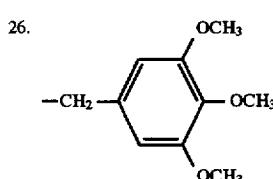
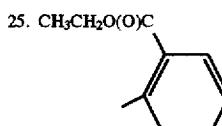
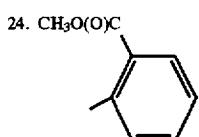
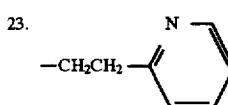
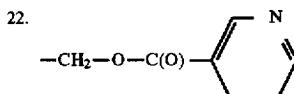
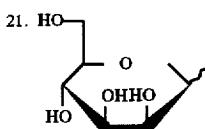
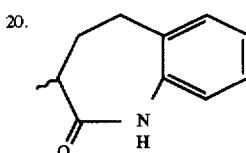
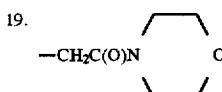
alkyl substituted by any of the groups set forth above for aryl, in particular OH or by 1 to 3 halo atoms (including —CH₃, —CH(CH₃)₂, —C(CH₃)₃, —CH₂CH₃, —(CH₂)₂CH₃, —(CH₂)₃CH₃, —(CH₂)₄CH₃, —(CH₂)₅CH₃, —CH₂CH₂F, —CH₂CH₂Cl, —CH₂CF₃, and —CH₂CCl₃);



20

TABLE A-continued

3. —CH₂—S(O)₂(R¹)
4. —CH₂—O—C(O)—CH₂—C₆H₅
5. 3-cholesteryl
6. 3-pyridyl
7. N-ethylmorpholino
8. —CH₂—O—C(O)—C₆H₅
9. —CH₂—O—C(O)—CH₂CH₃
10. —CH₂—O—C(O)—C(CH₃)₃
11. —CH₂—CCl₃
12. —C₆H₅
13. —NH—CH₂—C(O)O—CH₂CH₃
14. —N(CH₃)—CH₂—C(O)O—CH₂CH₃
15. —NHR¹
16. —CH₂—O—C(O)—C₁₀H₁₅
17. —CH₂—O—C(O)—CH(CH₃)₂
18. —CH₂—C#H(OC(O)CH₂R¹)—CH₂—(OC(O)CH₂R¹)*



#- chiral center is (R), (S) or racemate.

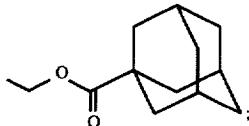
Other esters that are suitable for use herein are described in EP 632.048.

R₆₂ also includes alkyl- or aryl-acyloxyalkyl groups of the structure —CH₂O(CO)R₃₇ or —CH₂(CO)OR₃₈ (linked to oxygen of the acidic group) wherein R₃₇ and R₃₈ are alkyl, aryl, or alkylaryl groups (see U.S. Pat. No. 4,968,788).

TABLE A

1. —CH₂—C(O)—N(R¹)₂*
2. —CH₂—S(O)(R¹)

Frequently R_{37} and R_{38} are bulky groups such as branched alkyl, ortho-substituted aryl, meta-substituted aryl, or combinations thereof, including normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral administration. Examples of such useful R_{6a} groups are alkylacyloxymethyl esters and their derivatives, including



$-\text{CH}_2\text{OC(O)C}_{10}\text{H}_{15}$, $-\text{CH}_2\text{OC(O)C(CH}_3)_3$, $-\text{CH}(\text{CH}_2\text{OCH}_3)\text{OC(O)C(CH}_3)_3$, $-\text{CH}(\text{CH}(\text{CH}_3)_2)\text{OC(O)C(CH}_3)_3$, $-\text{CH}_2\text{OC(O)CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{OC(O)C}_6\text{H}_{11}$, $-\text{CH}_2\text{OC(O)C}_6\text{H}_5$, $-\text{CH}_2\text{OC(O)C}_{10}\text{H}_{15}$, $-\text{CH}_2\text{OC(O)CH}_2\text{CH}_3$, $-\text{CH}_2\text{OC(O)CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{OC(O)C(CH}_3)_3$ and $-\text{CH}_2\text{OC(O)CH}_2\text{C}_6\text{H}_5$.

R_{6a} , R_{6c} and R_{6b} groups optionally are used to prevent side reactions with the protected group during synthetic procedures, so they can function as protecting groups (PRT) during synthesis. For the most part the decision as to which groups to protect, when to do so, and the nature of the PRT will be dependent upon the chemistry of the reaction to be protected against (e.g., acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PRT groups do not need to be, and generally are not, the same if the compound is substituted with multiple PRT. In general, PRT will be used to protect carboxyl, hydroxyl or amino groups. The order of deprotection to yield free groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order.

A very large number of R_{6a} hydroxy protecting groups and R_{6c} amide-forming groups and corresponding chemical cleavage reactions are described in "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; "Protecting Groups" (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For R_{6a} carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for W_1 acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

In some embodiments the R_{6a} protected acidic group is an ester of the acidic group and R_{6a} is the residue of a hydroxyl-containing functionality. In other embodiments, an R_{6c} amino compound is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing functionalities are set forth above or are found in WO 95/07920. Of particular interest are the residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid, polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and related text of WO 95/07920 as groups L1 or L2, which is hereby incorporated by reference. WO 95/07920 expressly teaches the amidates of phosphonic acids, but it will be

understood that such amidates are formed with any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

Typical R_{6a} esters for protecting W_1 acidic functionalities are also described in WO 95/07920, again understanding that the same esters can be formed with the acidic groups herein as with the phosphonate of the '920 publication. Typical ester groups are defined at least on WO 95/07920 pages 89-93 (under R^{31} or R^{35}), the table on page 105, and pages 21-23 (as R). Of particular interest are esters of unsubstituted aryl such as phenyl or arylalkyl such benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl, especially phenyl, ortho-ethoxyphenyl, or C_1-C_4 alkylestercarboxyphenyl (salicylate C_1-C_{12} alkylesters).

15 The protected acidic groups W_1 , particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the W_1 acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds of the invention having protected groups, in particular amino acid amidates or substituted and unsubstituted aryl esters are administered systemically or orally they are capable of hydrolytic cleavage in vivo to yield the free acid.

20 25 One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is employed, e.g., the esters may be different or the same, or a mixed amide and ester may be used.

Typical R_{6a} hydroxy protecting groups described in Greene (pages 14-118) include Ethers (Methyl); Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, t-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzylloxymethyl, p-Methoxybenzylloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, t-Butoxymethyl, 4-Pentyloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis

(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, 40 Tetrahydropthiopyranyl, 1-Methoxycyclohexyl, 4-Methoxytetrahydrotetrahydropyranyl, 4-Methoxytetrahydrotetrahydropyranyl S,S-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 35, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3, 3a, 4, 5, 6, 7, 7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl); Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxethyl, 1-Methyl-1-

benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl, t-Butyl, Allyl, p-Chlorophenyl, p-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl); Substituted Benzyl Ethers (p-Methoxybenzyl, 3,4-Dimethoxybenzyl, o-Nitrobenzyl,

55 p-Nitrobenzyl, p-Halobenzyl, 2,6-Dichlorobenzyl, p-Cyanobenzyl, p-Phenylbenzyl, 2- and 4-Picolyl, 3-Methyl-2-picolyl N-Oxido, Diphenylmethyl, p,p'-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, α -Naphthylidiphenylmethyle, Di(p-methoxyphenyl)phenylmethyl, Tri(p-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenylidiphenylmethyl, 4,4',4"-Tris(4,

5-dichlorophthalimidophenyl)methyl, 4,4',4"-Tris(levulinoxyloxyphenyl)methyl, 4,4',4"-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',

4"-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-

5-methoxyphenyl)xanthenyl, 9-(9-Phenyl)phenanthrenyl, 9-(9-

5-methoxyphenyl)phenanthrenyl, 9-(9-Phenyl)phenanthrenyl, 9-(9-

5-methoxyphenyl)phenanthrenyl, 9-(9-Phenyl)phenanthrenyl, 9-(9-

5-methoxyphenyl)phenanthrenyl, 9-(9-Phenyl)phenanthrenyl, 9-(9-

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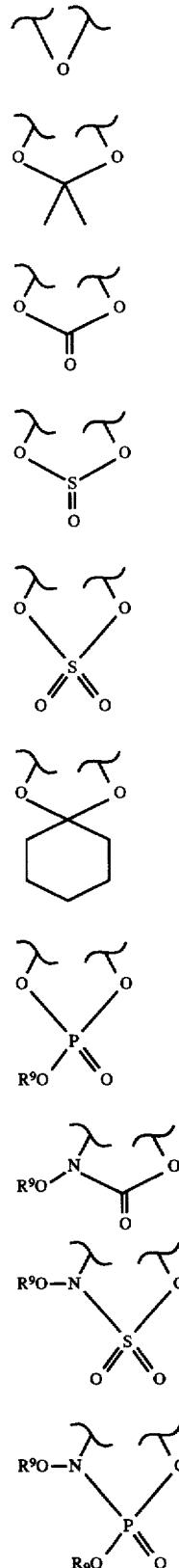
Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzoisothiazolyl S,S-Dioxido); Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsilyl, Dimethylhexylsilyl, ⁵ t-Butyldimethylsilyl, t-Butyldiphenylsilyl, Tribenzylsilyl, Tri-p-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, t-Butylmethoxyphenylsilyl); Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, ¹⁰ p-Chlorophenoxyacetate, p-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, ¹⁵ p-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate)); Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, p-Nitrophenyl, Benzyl, p-Methoxybenzyl, 3,4-Dimethoxybenzyl, o-Nitrobenzyl, p-Nitroenyl, S-Benzyl ²⁰ Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate); Groups, With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, o-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl ²⁵ Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate, ³⁰ Chorodiphenylacetate, Isobutyrate, Monosuccinate, (E)-2-Methyl-2-butenoate (Tiglate), o-(Methoxycarbonyl)benzoate, p-poly-Benzoate, α -Naphthoate, Nitrate, Alkyl N,N,N',N'-Tetramethylphosphorodiamide, ³⁵ N-Phenylcarbamate, Borate, Dimethylphosphinothiyl, 2,4-Dinitrophenylsulfonate); and Sulfonates (Sulfate, Methane-sulfonate (Mesylate), Benzylsulfonate, Tosylate).

More typically, R_{6a} hydroxy protecting groups include substituted methyl ethers, substituted benzyl ethers, silyl ethers, and esters including sulfonic acid esters, still more typically, trialkylsilyl ethers, tosylates and acetates. ⁴⁰

Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken together with the R_{6a} protecting functionality) are described in Greene at pages 118-142 and ⁴⁵ include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-t-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, ⁵⁰ p-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidene, 1,2-Dimethoxyethylidene, ⁵⁵ α -Methoxybenzylidene, 1-(N,N-Dimethylamino)ethylidene Derivative, α -(N,N-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl Derivatives (Di-t-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropylsiloxydisiloxanylidene), and Tetra-t-butoxydisiloxane-1,3-diylidene), Cyclic Carbonates, Cyclic ⁶⁰ Boronates, Ethyl Boronate and Phenyl Boronate.

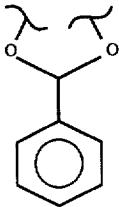
More typically, 1,2-diol protecting groups include those shown in Table B, still more typically, epoxides, acetonides, cyclic ketals and aryl acetals.

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-continued

wherein R^9 is C_1 – C_6 alkyl.

R_{6b} is H, a protecting group for amino or the residue of a carboxyl-containing compound, in particular H, —C(O)R₄, an amino acid, a polypeptide or a protecting group not —C(O)R₄, amino acid or polypeptide. Amide-forming R_{6b} are found for instance in group G₁. When R_{6b} is an amino acid or polypeptide it has the structure R₁₅NHCH(R₁₆)C(O)—, where R₁₅ is H, an amino acid or polypeptide residue, or R₅, and R₁₆ is defined below.

R₁₆ is lower alkyl or lower alkyl (C₁–C₆) substituted with amino, carboxyl, amide, carboxyl ester, hydroxyl, C₆–C₇ aryl, guanidinyl, imidazolyl, indolyl, sulphydryl, sulfoxide, and/or alkylphosphate. R₁₀ also is taken together with the amino acid α N to form a proline residue (R₁₀=—CH₂—). However, R₁₀ is generally the side group of a naturally-occurring amino acid such as H, —CH₃, —CH(CH₃)₂, —CH₂—CH(CH₃)₂, —CHCH₃—CH₂—CH₃, —CH₂—C₆H₅, —CH₂CF₂—S—CH₃, —CH₂OH, —CH(OH)—CH₃, —CH₂—SH, —CH₂—C₆H₄OH, —CH₂—CO—NH₂, —CH₂—CH₂—CO—NH₂, —CH₂—COOH, —(CH₂)₄—NH₂ and —(CH₂)₃—NH—C(NH₂)—NH₂. R₁₀ also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

R_{6b} are residues of carboxylic acids for the most part, but any of the typical amino protecting groups described by Greene at pages 315–385 are useful. They include Carbamates (methyl and ethyl, 9-fluorenylmethyl, 9(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl); Substituted Ethyl (2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenyl)ethyl, 1-(3,5-di-t-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(N,N-dicyclohexylcarboxamido)ethyl, t-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, N-hydroxypiperidinyl, alkylthio, benzyl, p-methoxybenzyl, p-nitrobenzyl, p-bromobenzyl, p-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl); Groups With Assisted Cleavage (2-methylthioethyl, 2-methylsulfonylethyl, 2-(p-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, m-chloro-p-acyloxybenzyl, p-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl); Groups Capable of Photolytic Cleavage (m-nitrophenyl, 3,5-dimethoxybenzyl, o-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(o-nitrophenyl)methyl); Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, N'-p-toluenesulfonylaminocarbonyl, N'-phenylaminothiocarbonyl); Miscellaneous Carbamates (t-amyl, S-benzyl thiocarbamate, p-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl,

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p-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, o-(N,N-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(N,N-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, p-(p'-Methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(p-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, p-(phenylazo)benzyl, 2,4,6-tri-t-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl); Amides (N-formyl, N-acetyl, N-chloroacetyl, N-trichloroacetyl, N-trifluoroacetyl, N-phenylacetyl, N-3-phenylpropionyl, N-picolinoyl, N-3-pyridylcarboxamide, N-benzoylphenylalanyl, N-benzoyl, N-p-phenylbenzoyl); Amides With Assisted Cleavage (N-o-nitrophenylacetyl, N-o-nitrophenoxyacetyl, N-acetoacetyl, (N'-dithiobenzylloxycarbonylamino)acetyl, N-3-(p-hydroxyphenyl)propionyl, N-3-(o-nitrophenyl)propionyl, N-2-methyl-2-(o-nitrophenoxy)propionyl, N-2-methyl-2-(o-phenylazophenoxy)propionyl, N-4-chlorobutryl, N-3-methyl-3-nitrobutryl, N-o-nitrocinnamoyl, N-acetylmethionine, N-o-nitrobenzoyl, N-o-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one); Cyclic Imide Derivatives (N-phthalimide, N-dithiasuccinoyl, N-2,3-diphenylmaleoyl, N-2,5-dimethylpyrrolyl, N-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl); N-Alkyl and N-Aryl Amines (N-methyl, N-allyl, N-[2-(trimethylsilyl)ethoxy]methyl, N-3-acetoxypropyl, N-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, N-benzyl, N-di(4-methoxyphenyl)methyl, N-5-dibenzosuberyl, N-triphenylmethyl, N-(4-methoxyphenyl)diphenylmethyl, N-9-phenylfluorenyl, N-2,7-dichloro-9-fluorenylmethylene, N-ferrocenylmethyl, N-2-picolyamine N'-oxide), Imine Derivatives (N-1,1-dimethylthiomethylene, N-benzylidene, N-p-methoxybenylidene, N-diphenylmethylene, N-[(2-pyridyl)methyl]methylene, N-(N',N'-dimethylaminomethylene, N,N'-isopropylidene, N-p-nitrobenzylidene, N-salicylidene, N-5-chlorosalicylidene, N-(5-chloro-2-hydroxyphenyl)phenylmethylene, N-cyclohexylidene); Enamine Derivatives (N-(5,5-dimethyl-3-oxo-1-cyclohexenyl)); N-Metal Derivatives (N-borane derivatives, N-diphenylborinic acid derivatives, N-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, N-copper or N-zinc chelate); N—N Derivatives (N-nitro, N-nitroso, N-oxide); N—P Derivatives (N-diphenylphosphinyl, N-dimethylthiophosphinyl, N-diphenylthiophosphinyl, N-dialkyl phosphoryl, N-dibenzyl phosphoryl, N-diphenyl phosphoryl); N—Si Derivatives; N—S Derivatives; N-Sulfonyl Derivatives (N-benzenesulfonyl, N-o-nitrobenzenesulfonyl, N-2,4-dinitrobenzenesulfonyl, N-pentachlorobenzenesulfonyl, N-2-nitro-4-methoxybenzenesulfonyl, N-triphenylmethylsulfonyl, N-3-nitropyridinesulfonyl); and N-Sulfonyl Derivatives (N-p-toluenesulfonyl, N-benzenesulfonyl, N-2,3,6-trimethyl-4-methoxybenzenesulfonyl, N-2,6-dimethyl-4-methoxybenzenesulfonyl, N-pentamethylbenzenesulfonyl, N-2,3,5,6-tetramethyl-4-methoxybenzenesulfonyl, N-4-methoxybenzenesulfonyl, N-2,4,6-trimethylbenzenesulfonyl, N-2,2,5,7,8-pentamethylchroman-

6-sulfonyl, N-methanesulfonyl, N- β -trimethylsilyethanesulfonyl, N-9-anthracenesulfonyl, N-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, N-benzylsulfonyl, N-trifluoromethylsulfonyl, N-phenacylsulfonyl).

More typically, protected amino groups include carbamates and amides, still more typically, $-\text{NHC(O)R}_1$ or $-\text{N}=\text{CR}_1\text{N}(\text{R}_1)_2$.

R_{6c} is H or the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, $-\text{NHSO}_2\text{R}_4$, NHC(O)R_4 , $-\text{N}(\text{R}_4)_2$, NH_2 or $-\text{NH}(\text{R}_4)(\text{H})$, whereby for example the carboxyl or phosphonic acid groups of W_1 are reacted with the amine to form an amide, as in $-\text{C(O)R}_{6c}$, $-\text{P(O)(R}_{6c})_2$ or $-\text{P(O)(OH)(R}_{6c})$. In general, R_{6c} has the structure $\text{R}_{17}\text{C(O)CH(R}_{16})\text{NH}-$, where R_{17} is OH, OR_{6a}, OR₅, an amino acid or a polypeptide residue.

Amino acids are low molecular weight compounds, on the order of less than about 1,000 MW, that contain at least one amino or imino group and at least one carboxyl group. Generally the amino acids will be found in nature, i.e., can be detected in biological material such as bacteria or other microbes, plants, animals or man. Suitable amino acids typically are alpha amino acids, i.e. compounds characterized by one amino or imino nitrogen atom separated from the carbon atom of one carboxyl group by a single substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono- or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not contain a sulphydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline.

When R_{6b} and R_{6c} are single amino acid residues or polypeptides they usually are substituted at R_3 , W_6 , W_1 and/or W_2 , but typically only W_1 or W_2 . These conjugates are produced by forming an amide bond between a carboxyl group of the amino acid (or C-terminal amino acid of a polypeptide for example) and W_2 . Similarly, conjugates are formed between W_1 and an amino group of an amino acid or polypeptide. Generally, only one of any site in the parental molecule is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. Usually, a carboxyl group of W_1 is amidated with an amino acid. In general, the α -amino or α -carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the parental functionalities, i.e., carboxyl or amino groups in the amino acid side chains generally are not used to form the amide bonds with the parental compound (although these groups may need to be protected during synthesis of the conjugates as described further below).

With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked e.g. by R_{6a} , esterified with R_5 or amidated with R_{6c} . Similarly, the amino side chains R_{16} optionally will be blocked with R_{6b} or substituted with R_5 .

Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable in vivo or in vitro under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments. The esters or amino acid or polypeptide amides also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid or polypeptide conjugates of this invention by conventional hydrolysis procedures.

When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D isomers are useful. On the other hand, L isomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R_{6b} and R_{6c} include the following:

Glycine;

Aminopolycarboxylic acids, e.g., aspartic acid, β -hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β -methylaspartic acid, β -methylglutamic acid, β,β -dimethylaspartic acid, γ -hydroxyglutamic acid, β,γ -dihydroxyglutamic acid, β -phenylglutamic acid, γ -methylene glutamic acid, 3-amino adipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid;

Amino acid amides such as glutamine and asparagine;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyric acid, ornithine, citrulline, homoarginine, homocitrulline, hydroxylysine, alhydroxylysine and diaminobutyric acid;

Other basic amino acid residues such as histidine;

Diaminodicarboxylic acids such as α,α' -diaminosuccinic acid, α,α' -diaminoglutamic acid, α,α' -diaminoadipic acid, α,α' -diaminopimelic acid, α,α' -diamino- β -hydroxypimelic acid, α,α' -diaminosuberic acid, α,α' -diaminoazelaic acid, and α,α' -diaminosebacic acid;

Imino acids such as proline, hydroxyproline, alhydroxyproline, γ -methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;

A mono- or di-alkyl (typically C_1 – C_8 branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyric acid, norvaline, norleucine, heptyline, α -methylserine, α -amino- α -methyl- γ -hydroxyvaleric acid, α -amino- α -methyl- δ -hydroxyvaleric acid, α -amino- α -methyl- ϵ -hydroxycaprylic acid, isovaline, α -methylglutamic acid, α -aminoisobutyric acid, α -aminodiethylacetic acid, α -aminodiisopropylacetic acid, α -aminodi-n-propylacetic acid, α -aminodisobutylic acid, α -aminodi-n-butylacetic acid, α -aminoethylisopropylacetic acid, α -amino-n-propylacetic acid, (α -aminodiisoamylacetic acid, α -methylaspartic acid, α -methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, alloisoleucine, tert-leucine, β -methyltryptophan and α -amino- β -ethyl- β -phenylpropionic acid;

β -phenylserinyl;

Aliphatic α -amino- β -hydroxy acids such as serine, β -hydroxyleucine, β -hydroxynorleucine, β -hydroxynorvaline, and α -amino- β -hydroxystearic acid;

α -Amino, α -, γ -, δ - or ϵ -hydroxy acids such as homoserine, γ -hydroxynorvaline, δ -hydroxynorvaline and epsilon-hydroxynorleucine residues; canavine and cananine; γ -hydroxyornithine;

2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;

α -Amino- β -thiols such as penicillamine, β -thiolnorvaline or β -thiolbutyryne;

Other sulfur containing amino acid residues including cysteine: homocysteine, β -phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine;

Phenylalanine, tryptophan and ring-substituted α amino acids such as the phenyl- or cyclohexylamino acids α -aminophenylacetic acid, α -aminocyclohexylacetic acid and α -amino- β -cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methoxytyrosine and o-chloro-, p-chloro-, 3,4-dichloro, o-, m- or p-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thiethyl-, pyridyl-, pyrimidinyl-, purinyl- or naphthylalanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan;

α -Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and

α -Hydroxy and substituted α -hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine.

Polypeptides are polymers of amino acids in which a carboxyl group of one amino acid monomer is bonded to an amino or imino group of the next amino acid monomer by an amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about 1500-5000 MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more residues, and suitably are substantially sequence-homologous with human, animal, plant or microbial proteins. They include enzymes (e.g., hydrogen peroxidase) as well as immunogens such as KLH, or antibodies or proteins of any type against which one wishes to raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amides are useful as immunogens in raising antibodies against either the polypeptide (if it is not immunogenic in the animal to which it is administered) or against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to separate the parental compound from mixtures, for example in diagnosis or manufacturing of the parental compound. The conjugates of parental compound and polypeptide generally are more immunogenic than the polypeptides in closely homologous animals, and therefore make the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the

polypeptide or protein may not need to be immunogenic in an animal typically used to raise antibodies, e.g., rabbit, mouse, horse, or rat, but the final product conjugate should be immunogenic in at least one of such animals. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, e.g. a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases. Carboxypeptidases digest polypeptides by removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide (having a given pair of residues and a free carboxyl terminus) is covalently bonded through its α -amino group to the phosphorus or carbon atoms of the compounds herein. In embodiments where W_1 is phosphonate it is expected that this peptide will be cleaved by the appropriate peptidolytic enzyme, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the phosphonoamidate bond.

Suitable dipeptidyl groups (designated by their single letter code) are AA, AR, AN, AD, AC, AE, AQ, AG, AH, AL, AL, AK, AM, AF, AP, AS, AT, AW, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RL, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HL, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, KQ, KG, KH, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN, TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW, YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT, VW, VY and VV.

Tripeptide residues are also useful as R_{6b} or R_{6c} . When W_1 is phosphonate, the sequence -X4-pro-X5- (where X4 is any amino acid residue and X5 is an amino acid residue, a carboxyl ester of proline, or hydrogen) will be cleaved by luminal carboxypeptidase to yield X4 with a free carboxyl, which in turn is expected to autocatalytically cleave the phosphonoamidate bond. The carboxy group of X5 optionally is esterified with benzyl.

Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to

peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α -amino group are transport substrates for the peptide transporter found in brush border membrane of intestinal mucosal cells (Bai, J. P. F., "Pharm Res." 9:969-978 (1992). Transport competent peptides can thus be used to enhance bioavailability of the amide compounds. Di- or tripeptides having one or more amino acids in the D configuration are also compatible with peptide transport and can be utilized in the amide compounds of this invention. Amino acids in the D configuration can be used to reduce the susceptibility of a di- or tripeptide to hydrolysis by proteases common to the brush border such as aminopeptidase N (EC 3.4.11.2). In addition, di- or tripeptides alternatively are selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or polypeptides lacking asp and/or glu are poor substrates for aminopeptidase A (EC 3.4.11.7), di- or tripeptides lacking amino acid residues on the N-terminal side of hydrophobic amino acids (leu, tyr, phe, val, tip) are poor substrates for endopeptidase 24.11 (EC 3.4.24.11), and peptides lacking a pro residue at the penultimate position at a free carboxyl terminus are poor substrates for carboxypeptidase P (EC 3.4.17). Similar considerations can also be applied to the selection of peptides that are either relatively resistant or relatively susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases. Such poorly cleaved polypeptide amides are immunogens or are useful for bonding to proteins in order to prepare immunogens.

Stereoisomers

The compounds of the invention are enriched or resolved optical isomers at any or all asymmetric atoms. For example, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diasteromeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

Exemplary stereochemistry of the compounds of this invention is set forth below in Table C.

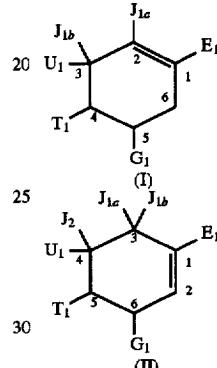
TABLE C

Formula (I)					
E_1	J_{1a}	J_{1b}	U_1	T_1	G_1
—	—	α	β	α	α
—	—	β	α	α	α
—	—	α	β	β	α
—	—	α	β	α	β
		β	α	β	α
		β	α	α	β
		α	β	β	β
		β	α	β	β
—	α	β	α	α	α
—	β	α	β	β	β

E_1	J_{1a}	J_{1b}	J_2	U_1	T_1	G_1
—	α	β	α	β	α	α

TABLE C-continued

Formula (I)							
5	—	β	α	α	β	α	α
—	—	α	β	β	α	α	α
—	—	α	β	α	β	β	α
—	—	α	β	α	β	α	β
10	—	β	α	β	α	α	α
—	—	β	α	α	β	β	α
—	—	α	β	β	α	α	β
—	—	α	β	α	β	β	β
15	—	β	α	β	β	α	β
—	—	α	β	β	α	β	β
—	—	β	α	β	β	β	α
—	—	β	α	β	β	β	β



The compounds of the invention can also exist as tautomeric isomers in certain cases. For example, ene-amine tautomers can exist for imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+ , Li^+ , K^+ , Ca^{++} and Mg^{++} . Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically the W_1 group carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

50 Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+ , Na^+ , and K^+ . A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g., HCl , HBr , H_2SO_4 , or organic sulfonic acids, to basic centers, typically amines of group G_1 , or to acidic groups such as E_1 . Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

60 65 Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any of the amino acids described above are suitable,

especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Methods of Inhibition of Neuraminidase

Another aspect of the invention relates to methods of inhibiting the activity of neuraminidase comprising the step of treating a sample suspected of containing neuraminidase with a compound of the invention.

Compositions of the invention act as inhibitors of neuraminidase, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of neuraminidase having a geometry unique to neuraminidase. Compositions binding neuraminidase may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of neuraminidase. Accordingly, the invention relates to methods of detecting neuraminidase in a sample suspected of containing neuraminidase comprising the steps of: treating a sample suspected of containing neuraminidase with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl or amino.

Within the context of the invention samples suspected of containing neuraminidase include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces neuraminidase, frequently a pathogenic organism such as a virus. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of neuraminidase after application of the composition can be observed by any method including direct and indirect methods of detecting neuraminidase activity. Quantitative, qualitative, and semiquantitative methods of determining neuraminidase activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain neuraminidase include bacteria (*Vibrio cholerae*, *Clostridium perfringens*, *Streptococcus pneumoniae*, and *Arthrobacter sialophilus*) and viruses (especially orthomyxoviruses or paramyxoviruses such as influenza virus A and B, parainfluenza virus, mumps virus,

Newcastle disease virus, fowl plague virus, and sendai virus). Inhibition of neuraminidase activity obtained from or found within any of these organisms is within the objects of this invention. The virology of influenza viruses is described in "Fundamental Virology" (Raven Press, New York, 1986), Chapter 24. The compounds of this invention are useful in the prophylaxis of influenza infections or treatment of existing influenza infections in animals such as duck, rodents, or swine, or in man.

Screens for Neuraminidase Inhibitors

Compositions of the invention are screened for inhibitory activity against neuraminidase by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of neuraminidase in vitro and compositions showing inhibitory activity are then screened for activity in vivo. Compositions having in vitro K_i (inhibitory constants) of less than about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for in vivo use.

Useful in vitro screens have been described in detail and will not be elaborated here. However, Itzstein, M. von et al.; "Nature", 363(6428):418-423 (1993), in particular page 420, column 2, full paragraph 3, to page 421, column 2, first partial paragraph, describes a suitable in vitro assay of Potier, M.; et al.; "Analyst Biochem.", 94:287-296 (1979), as modified by Chong, A. K. J.; et al.; "Biochem. Biophys. Acta", 1077:65-71 (1991); and Colman, P. M.; et al.; International Publication No. WO 92/06691 (Int. App. No. PCT/AU90/00501, publication date Apr. 30, 1992) page 34, line 13, to page 35, line 16, describes another useful in vitro screen.

In vivo screens have also been described in detail, see Itzstein, M. von et al.; op. cit., in particular page 421, column 2, first full paragraph, to page 423, column 2, first partial paragraph, and Colman, P. M.; et al.; op. cit. page 36, lines 1-38, describe suitable in vivo screens.

Pharmaceutical Formulations and Routes of Administration

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986), which is expressly incorporated by reference in its entirety. Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed

orally; it is not necessary to administer them by intrapulmonary or intranasal routes.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and, intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration are prepared as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of influenza A or B infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active influenza infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about 0.01 to about 5 mg/kg body weight per day. More typically, from about 0.05 to about 0.5 mg/kg body weight per day. For example, for inhalation the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Active ingredients of the invention are also used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating viral infections of the respiratory system, in particular influenza infection, the compositions of the invention are combined with anti-virals (such as amantadine, rimantadine and ribavirin), mucolytics, expectorants, bronchialdilators, antibiotics, antipyretics, or analgesics. Ordinarily, antibiotics, antipyretics, and analgesics are administered together with the compounds of this invention.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the in vivo metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. C¹⁴ or H³) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found in vivo, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no neuraminidase inhibitory activity of their own.

Additional Uses for the Compounds of This Invention

The compounds of this invention, or the biologically active substances produced from these compounds by hydrolysis or metabolism in vivo, are used as immunogens or for conjugation to proteins, whereby they serve as components of immunogenic compositions to prepare antibodies capable of binding specifically to the protein, to the compounds or to their metabolic products which retain immunologically recognized epitopes (sites of antibody binding). The immunogenic compositions therefore are useful as intermediates in the preparation of antibodies for use in diagnostic, quality control, or the like, methods or in assays for the compounds or their novel metabolic products. The compounds are useful for raising antibodies against otherwise non-immunogenic polypeptides, in that the compounds serve as haptic sites stimulating an immune response that cross-reacts with the unmodified conjugated protein.

The hydrolysis products of interest include products of the hydrolysis of the protected acidic and basic groups discussed above. As noted above, the acidic or basic amides comprising immunogenic polypeptides such as albumin or keyhole limpet hemocyanin generally are useful as immunogens. The metabolic products described above may retain a substantial degree of immunological cross reactivity with the compounds of the invention. Thus, the antibodies of this invention will be capable of binding to the unprotected compounds of the invention without binding to the protected compounds; alternatively the metabolic products, will be capable of binding to the protected compounds and/or the metabolic products without binding to the protected compounds of the invention, or will be capable of binding specifically to any one or all three. The antibodies desirably will not substantially cross-react with naturally-occurring materials. Substantial cross-reactivity is reactivity under

specific assay conditions for specific analytes sufficient to interfere with the assay results.

The immunogens of this invention contain the compound of this invention presenting the desired epitope in association with an immunogenic substance. Within the context of the invention such association means covalent bonding to form an immunogenic conjugate (when applicable) or a mixture of non-covalently bonded materials, or a combination of the above. Immunogenic substances include adjuvants such as Freund's adjuvant, immunogenic proteins such as viral, bacterial, yeast, plant and animal polypeptides, in particular keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin or soybean trypsin inhibitor, and immunogenic polysaccharides. Typically, the compound having the structure of the desired epitope is covalently conjugated to an immunogenic polypeptide or polysaccharide by the use of a polyfunctional (ordinarily bifunctional) cross-linking agent. Methods for the manufacture of hapten immunogens are conventional per se, and any of the methods used heretofore for conjugating haptens to immunogenic polypeptides or the like are suitably employed here as well, taking into account the functional groups on the precursors or hydrolytic products which are available for cross-linking and the likelihood of producing antibodies specific to the epitope in question as opposed to the immunogenic substance.

Typically the polypeptide is conjugated to a site on the compound of the invention distant from the epitope to be recognized.

The conjugates are prepared in conventional fashion. For example, the cross-linking agents N-hydroxysuccinimide, succinic anhydride or alkN=C=Nalk are useful in preparing the conjugates of this invention. The conjugates comprise a compound of the invention attached by a bond or a linking group of 1-100, typically, 1-25, more typically 1-10 carbon atoms to the immunogenic substance. The conjugates are separated from starting materials and by products using chromatography or the like, and then are sterile filtered and vialled for storage.

The compounds of this invention are cross-linked for example through any one or more of the following groups: a hydroxyl group of U_1 ; a carboxyl group of E_1 ; a carbon atom of U_1 , E_1 , G_1 , or T_1 , in substitution of H; and an amine group of G_1 . Included within such compounds are amides of polypeptides where the polypeptide serves as an above-described R_{6c} or R_{6b} groups.

Animals are typically immunized against the immunogenic conjugates or derivatives and antisera or monoclonal antibodies prepared in conventional fashion.

The compounds of the invention are useful for maintaining the structural integrity of glycoproteins in recombinant cell culture, i.e., they are added to fermentations in which glycoproteins are being produced for recovery so as to inhibit neuraminidase-catalyzed cleavage of the desired glycoproteins. This is of particular value in the recombinant synthesis of proteins in heterologous host cells that may disadvantageously degrade the carbohydrate portion of the protein being synthesized.

The compounds of the invention are polyfunctional. As such they represent a unique class of monomers for the synthesis of polymers. By way of example and not limitation, the polymers prepared from the compounds of this invention include polyamides and polyesters.

The present compounds are used as monomers to provide access to polymers having unique pendent functionalities. The compounds of this invention are useful in

homopolymers, or as comonomers with monomers which do not fall within the scope of the invention. Homopolymers of the compounds of this invention will have utility as cation exchange agents (polyesters or polyamides) in the preparation of molecular sieves (polyamides), textiles, fibers, films, formed articles and the like where the acid functionality E_1 is esterified to a hydroxyl group in U_1 , for example, whereby the pendant basic group G_1 is capable of binding acidic functionalities such as are found in polypeptides whose purification is desired. Polyamides are prepared by cross-linking E_1 and G_1 , with U_1 and the adjacent portion of the ring remaining free to function as a hydrophilic or hydrophobic affinity group, depending up the selection of the U_1 group. The preparation of these polymers from the compounds of the invention is conventional per se.

The compounds of the invention are also useful as a unique class of polyfunctional surfactants. Particularly when U_1 does not contain a hydrophilic substituent and is, for example, alkyl or alkoxy, the compounds have the properties of bi-functional surfactants. As such they have useful surfactant, surface coating, emulsion modifying, rheology modifying and surface wetting properties.

As polyfunctional compounds with defined geometry and carrying simultaneously polar and non-polar moieties, the compounds of the invention are useful as a unique class of phase transfer agents. By way of example and not limitation, the compounds of the invention are useful in phase transfer catalysis and liquid/liquid ion extraction (LIX).

The compounds of the invention optionally contain asymmetric carbon atoms in groups U_1 , E_1 , G_1 , and T_1 . As such, they are a unique class of chiral auxiliaries for use in the synthesis or resolution of other optically active materials. For example, a racemic mixture of carboxylic acids can be resolved into its component enantiomers by: 1) forming a mixture of diastereomeric esters or amides with a compound of the invention wherein U_1 is an asymmetric hydroxylalkane or amino alkane group; 2) separating the diastereomers; and 3) hydrolyzing the ester structure. Racemic alcohols are separated by ester formation with an acid group of E_1 . Further, such a method can be used to resolve the compounds of the invention themselves if optically active acids or alcohols are used instead of racemic starting materials.

The compounds of this invention are useful as linkers or spacers in preparing affinity absorption matrices, immobilized enzymes for process control, or immunoassay reagents.

The compounds herein contain a multiplicity of functional groups that are suitable as sites for cross-linking desired substances. For example, it is conventional to link affinity reagents such as hormones, peptides, antibodies, drugs, and the like to insoluble substrates. These insolublized reagents are employed in known fashion to absorb binding partners for the affinity reagents from manufactured preparations, diagnostic samples and other impure mixtures. Similarly, immobilized enzymes are used to perform catalytic conversions with facile recovery of enzyme. Bifunctional compounds are commonly used to link analytes to detectable groups in preparing diagnostic reagents.

Many functional groups in the compounds of this invention are suitable for use in cross-linking. For example, the carboxylic or phosphonic acid of group E_1 is used to form esters with alcohols or amides with amines of the reagent to be cross-linked. The G_1 sites substituted with OH, NHR₁, SH, azido (which is reduced to amino if desired before cross-linking), CN, NO₂, amino, guanidino, halo and the like are suitable sites. Suitable protection of reactive groups will be used where necessary while assembling the cross-

linked reagent to prevent polymerization of the bifunctional compound of this invention. In general, the compounds here are used by linking them through carboxylic or phosphonic acid to the hydroxyl or amino groups of the first linked partner, then covalently bonded to the other binding partner through a T₁ or G₁ group. For example a first binding partner such as a steroid hormone is esterified to the carboxylic acid of a compound of this invention and then this conjugate is cross-linked through a G₁ hydroxyl to cyanogen bromide activated Sepaharose, whereby immobilized steroid is obtained. Other chemistries for conjugation are well known. See for example Maggio, "Enzyme-Immunoassay" (CRC, 1988, pp 71-135) and references cited therein.

As noted above, the therapeutically useful compounds of this invention in which the W₁, or G₁ carboxyl, hydroxyl or amino groups are protected are useful as oral or sustained release forms. In these uses the protecting group is removed in vivo, e.g., hydrolyzed or oxidized, so as to yield the free carboxyl, amino or hydroxyl. Suitable esters or amides for this utility are selected based on the substrate specificity of esterases and/or carboxypeptidases expected to be found within cells where precursor hydrolysis is desired. To the extent that the specificity of these enzymes is unknown, one will screen a plurality of the compounds of this invention until the desired substrate specificity is found. This will be apparent from the appearance of free compound or of antiviral activity. One generally selects amides or esters of the invention compound that are (i) not hydrolyzed or hydrolyzed comparatively slowly in the upper gut, (ii) gut and cell permeable and (iii) hydrolyzed in the cell cytoplasm and/or systemic circulation. Screening assays preferably use cells from particular tissues that are susceptible to influenza infection, e.g. the mucous membranes of the bronchopulmonary tract. Assays known in the art are suitable for determining in vivo bioavailability including intestinal lumen stability, cell permeation, liver homogenate stability and plasma stability assays. However, even if the ester, amide or other protected derivatives are not converted in vivo to the free carboxyl, amino or hydroxyl groups, they remain useful as chemical intermediates.

Exemplary Methods of Making the Compounds of the Invention

The invention also relates to methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in "Compendium of Organic Synthetic Methods" (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, Jr. 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., "Advanced Organic Chemistry, Third Edition", (John Wiley & Sons, New York, 1985), "Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes", Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

A number of exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

Generally, the reaction conditions such as temperature, reaction time, solvents, workup procedures, and the like,

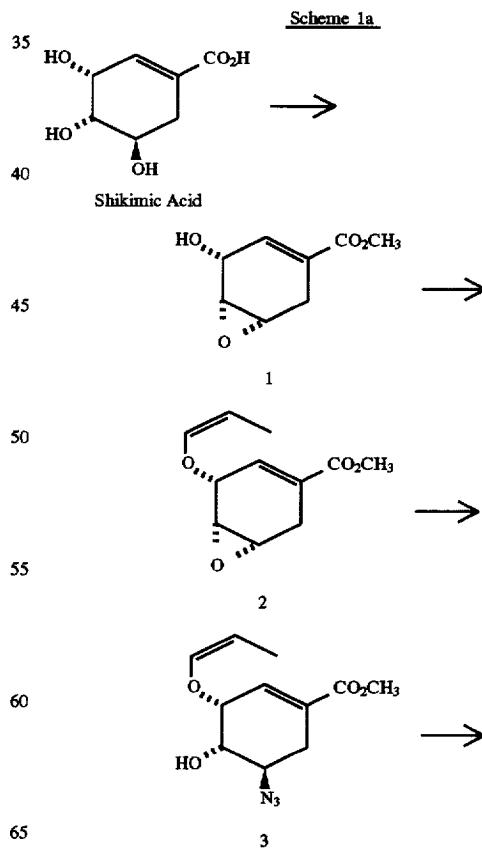
will be those common in the art for the particular reaction to be performed. The incorporated reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100° C. to 200° C., solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Workup typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20° C.), although for metal hydride reductions frequently the temperature is reduced to 0° C. to -100° C., solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0° C. to -100° C.) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g. inert gas environments) are common in the art and will be applied when applicable.

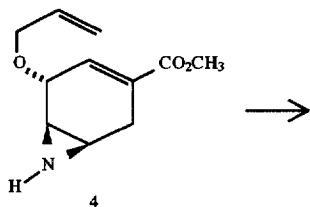
One exemplary method of preparing the compounds of the invention is shown in Schemes 1a and 1b below. A detailed description of the methods is found in the Experimental section below.



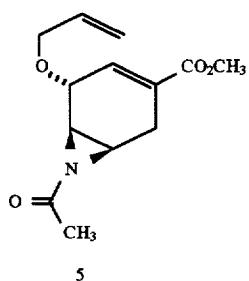
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-continued
Scheme 1a



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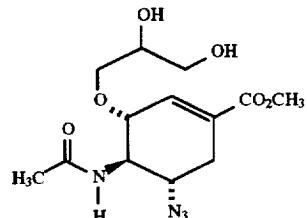
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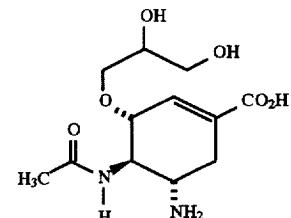
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Scheme 1b

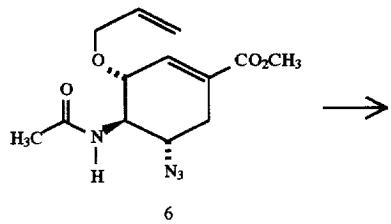


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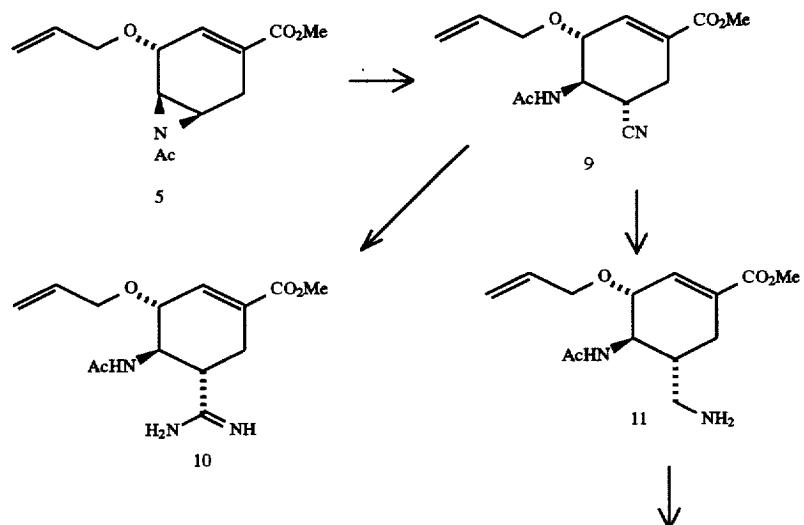
Scheme 1b



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30 Modifications of Schemes 1a and 1b to form additional embodiments is shown in Schemes 2-4.

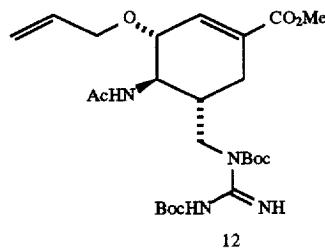
Scheme 2



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-continued
Scheme 2



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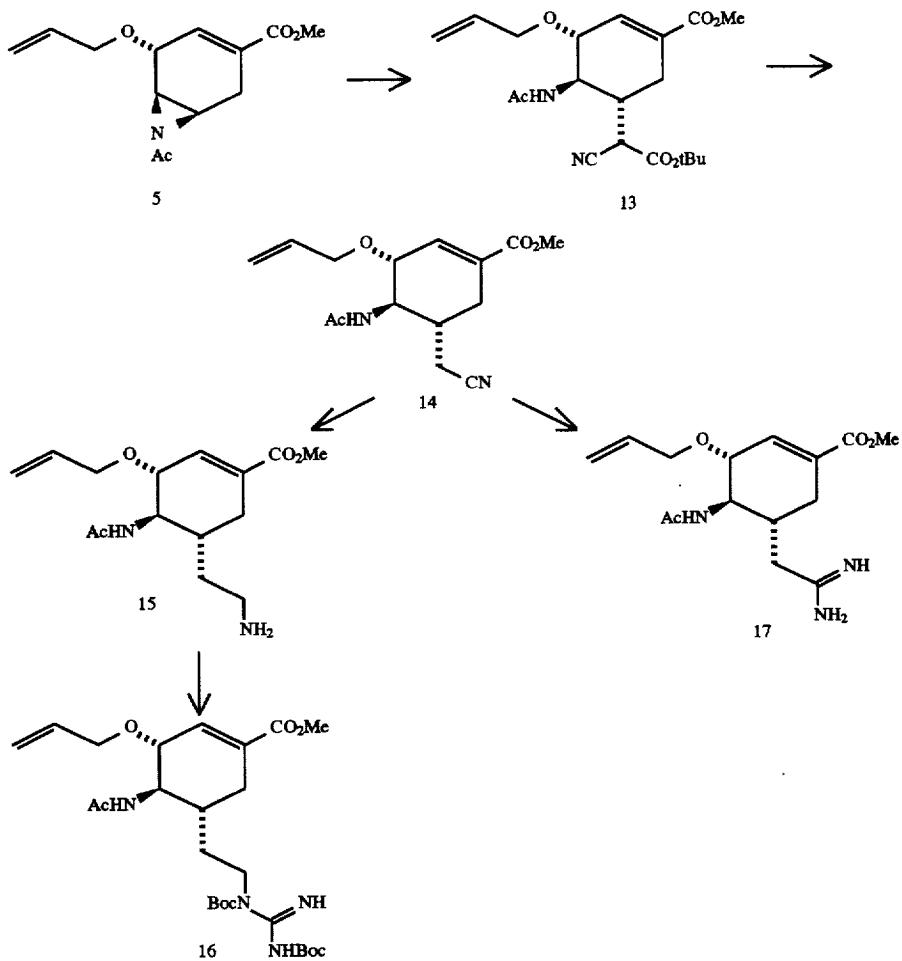
15 Nitrile 9 is converted to the amino methyl compound 11 by reduction using any of the available methods found in "Modern Synthetic Reactions" 2nd ed. H.O. House, Benjamin/Cummings Publishing Co., 1972.

20 Amino methyl compound 11 is converted to the bis-Boc protected guanidino compound 12 by treating 11 with N,N'-bis-Boc-1H-pyrazole-1-carboxamidine according to the method found in "Tetrahedron Lett.", 36:299 (1995).

Scheme 2

Aziridine 5 is converted to the amino nitrile 9 by $\text{Yb}(\text{CN})_3$ catalyzed addition of TMSCN according to the procedure of Utimoto and co-workers. "Tetrahedron Lett.", 31:6379 (1990).

Conversion of nitrile 9 to the corresponding amidine 10 is accomplished using a standard three step sequence: i) H_2S ; ii) CH_3I ; iii) NH_4OAc . A typical conversion is found in "J. Med. Chem.", 36:1811 (1993).

Scheme 3

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Scheme 3

The aziridine 5 is opened with α -cyano acetic acid t-butyl ester to give 13. Aziridine openings of this type are found in "Tetrahedron Lett.", 23:5021 (1982). Selective hydrolysis of the t-butyl ester moiety under acidic conditions followed by decarboxylation gives nitrile 14.

Reduction of 14 to the amino ethyl derivative 15 is accomplished in the same fashion as the conversion of 9 to 11. The amine 15 is then converted into the guanidino derivative 16 with *N,N'*-bis-Boc-1*H*-pyrazole-1-carboxamidine according to the method found in "Tetrahedron Lett.", 36:299 (1995).

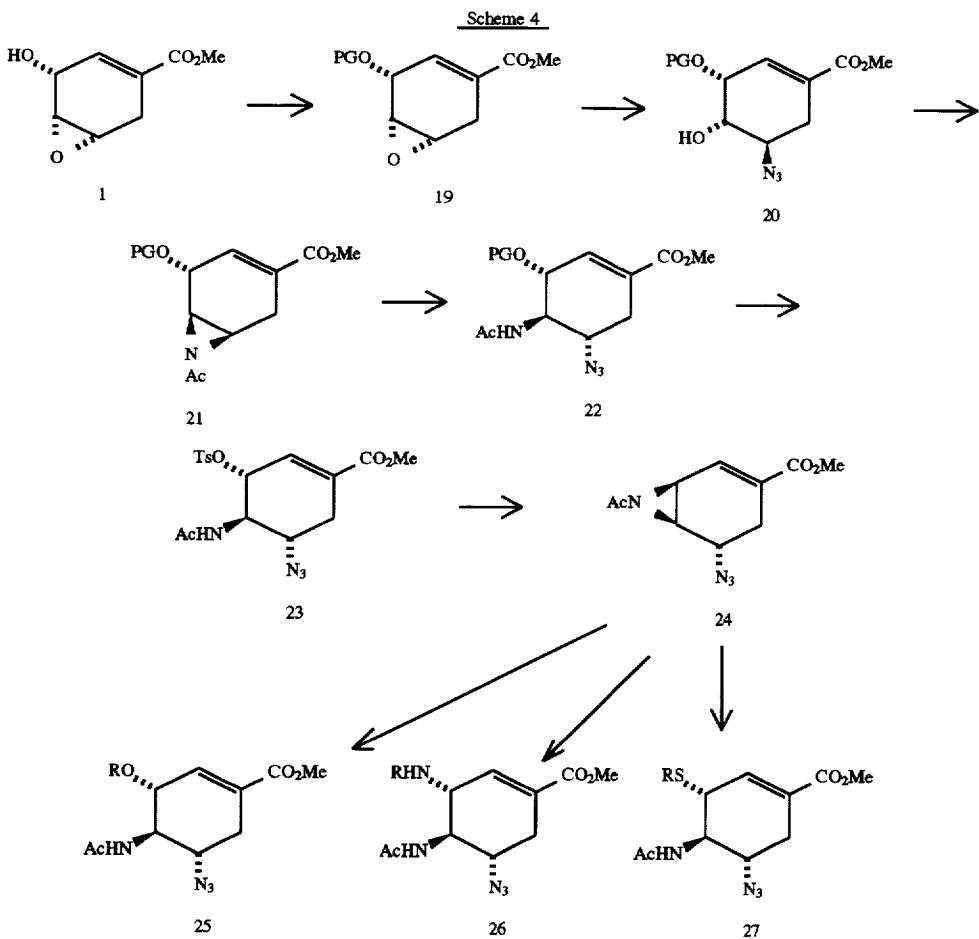
The nitrile 14 is converted to the corresponding amidine 17 using the same sequence described above for the conversion of 9 to 10.

48

Aziridine 21 is converted to the azido amide 22 by opening with $\text{NaN}_3/\text{NH}_4\text{Cl}$ in DMF at 65°C as described in "J. Chem. Soc. Perkin Trans I", 801 (1976).

Removal of the MOM protecting group of 22 is accomplished using the methods described in "Protective Groups in Organic Synthesis" 2nd ed., T. W. Greene and P. G. M. Wuts, John Wiley & Sons, New York, N.Y., 1991. The resulting alcohol is converted directly to aziridine 24 with TsCl in pyridine. Such transformations are found in "Angew. Chem. Int. Ed. Engl.", 33:599 (1994).

Aziridine 24 is then reacted with ROH, RNH₂ or RSH to give the corresponding ring opened derivatives 25, 26 and 27, respectively. Aziridine openings of this type are found in "Tetrahedron Lett.", 23:5021 (1982) and "Angew. Chem. Int. Ed. Engl.", 33:599 (1994).



Scheme 4

The epoxy alcohol 1 is protected (PG=protecting group), for example with MOMCl. Typical conditions are found in "Protective Groups in Organic Synthesis" 2nd ed., T. W. Greene and P. G. M. Wuts, John Wiley & Sons, New York, N.Y., 1991.

The epoxide 19 is opened with $\text{NaN}_3/\text{NH}_4\text{Cl}$ to the amino alcohol 20 according to the procedure of Sharpless and co-workers, "J. Org. Chem.", 50:1557 (1985).

Reduction of 20 to the N-acetyl aziridine 21 is accomplished in a three step sequence: 1) MsCl /triethyl amine; 2) H_2/Pd ; 3) AcCl /pyridine. Such transformations can be found in "Angew. Chem. Int. Ed. Engl.", 33:599 (1994).

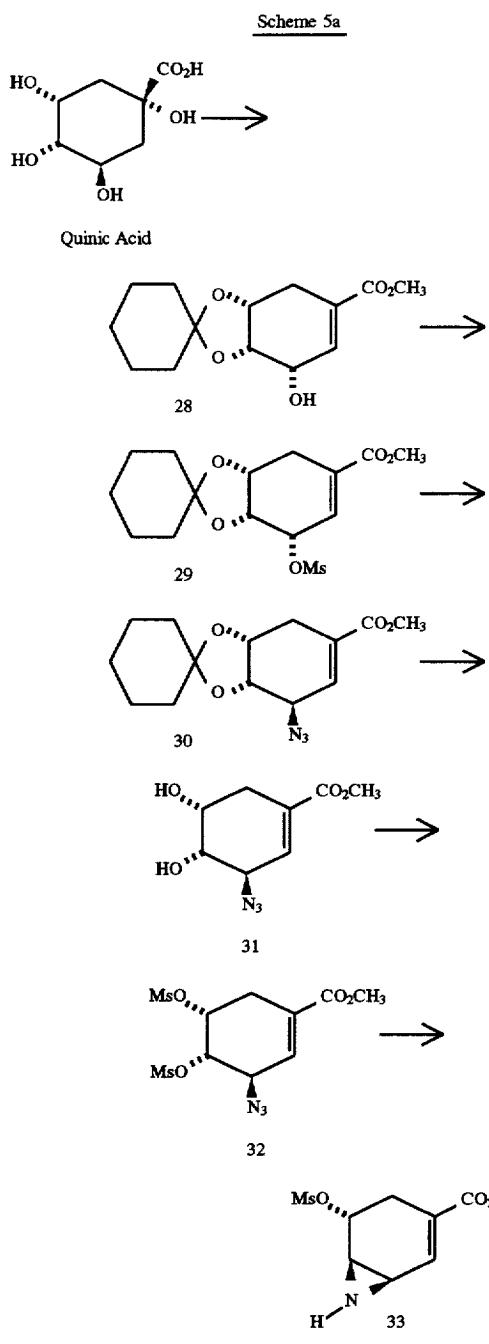
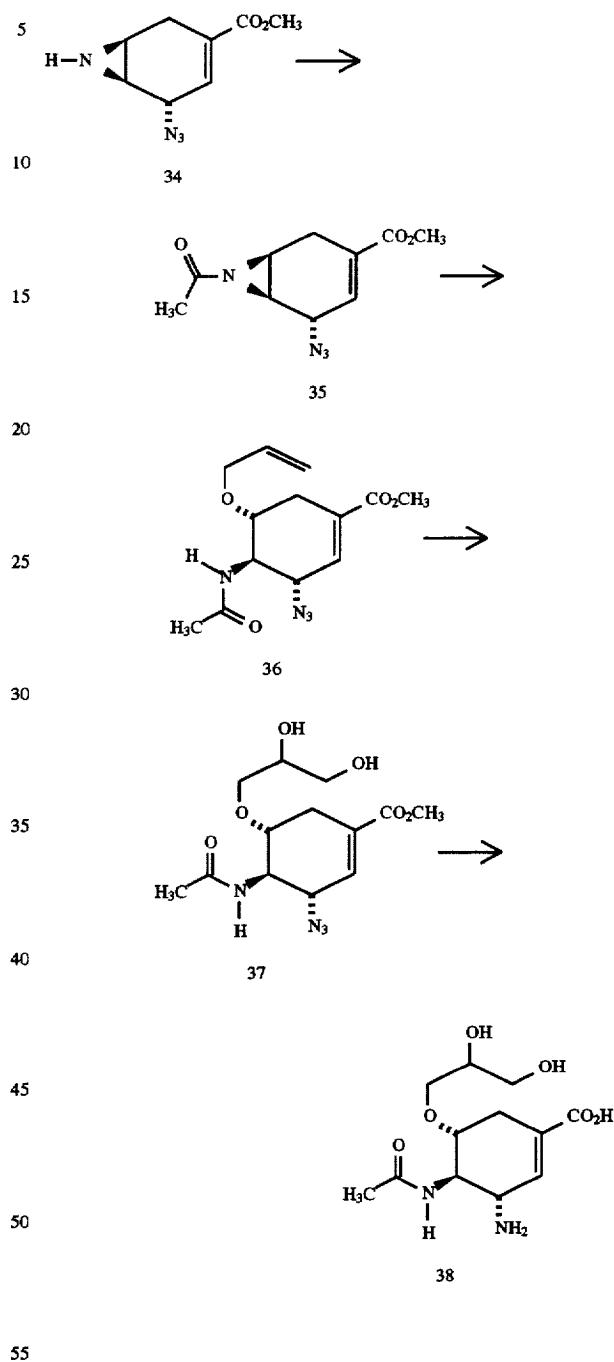
55 Scheme 5

Another class of compounds of the invention are prepared by the method of Schemes 5a and 5b. Quinic acid is converted to 28 by the method of Shing, T. K. M.; et al.; "Tetrahedron", 47(26):4571 (1991). Mesylation with MsCl in TEA/CH₂Cl₂ will give 29 which is reacted with NaN_3 in DMF to give 30. Reaction of 30 with TFA in CH₂Cl₂ will give 31 which is mesylated with MsCl in TEA/CH₂Cl₂ to give 32. Reaction with triphenylphosphine in water will give 33 which is converted to 35 by sequential application of: 1) $\text{CH}_3\text{C}(\text{O})\text{Cl}$ in pyridine, 2) NaN_3 in DMF, and 3) NaH in THF. Alkylation of 35 with a wide variety of nucleophiles common in the art will provide a number of compounds such

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as 36. Methods for elaboration of the compounds such as 36 to other embodiments of the invention will be similar to those described above.

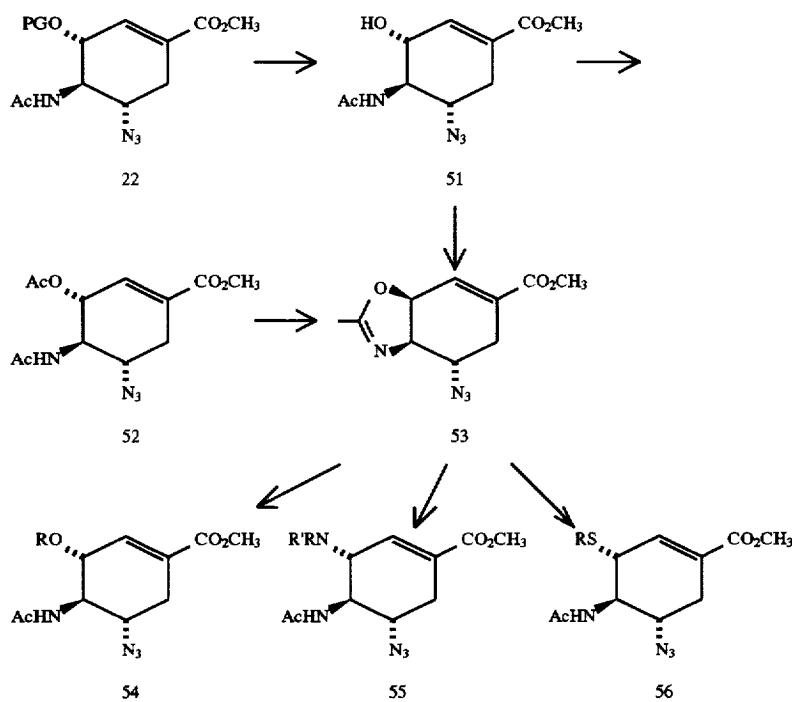
**50**Scheme 5b

5,763,483

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Scheme 6



Scheme 6

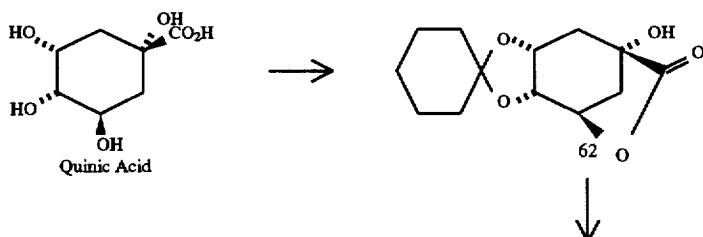
Another class of compounds of the invention are prepared by the method of Scheme 6. Protected alcohol 22 (PG=methoxymethyl ether) is deprotected under standard conditions described in "Protective Groups in Organic Synthesis" 2nd ed., T. W. Greene and P. G. M. Wuts, John Wiley & Sons, New York, N.Y., 1991. Alcohol 51 is converted to acetate 52 with acetic anhydride and pyridine under standard conditions. Acetate 52 is treated with TMSOTf or $\text{BF}_3\cdot\text{OEt}$ to afford oxazoline 53. Such transformations are described in "Liebigs Ann. Chem.", 129 (1991) and "Carbohydrate Research", 181 (1993), respectively. Alternatively, alcohol 51 is transformed to oxazoline 53 by conversion to the corresponding mesylate or tosylate 23 and subsequently cyclized to the oxazoline under standard conditions, as described in "J. Org. Chem.", 50:1126 (1985) and "J. Chem.

Soc.", 1385 (1970). Oxazoline 53 is reacted with ROH, RR'NH, or RSH (wherein R and R' are selected to be consistent with the definition of W_6 above) provide the corresponding ring opened derivatives 54, 55, and 56 respectively. Such transformations are described in "J. Org. Chem.", 49:4889 (1984) and "Chem. Rev.", 71:483 (1971).

40 Schemes 7-35

Other exemplary methods of preparing the compounds of the invention are shown in Schemes 7-35 below. A detailed description of the methods is found in the Experimental section below.

Scheme 7a

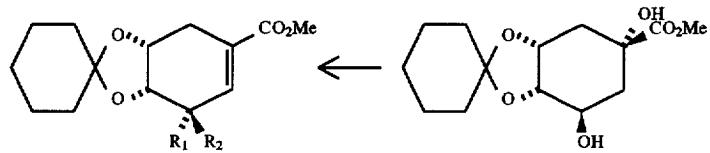


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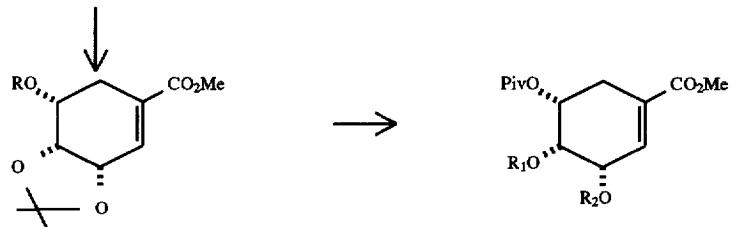
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-continued
Scheme 7a



64 $R_1 = R_2 = O$
28 $R_1 = OH, R_2 = H$

63



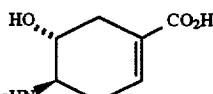
66 $R = H$
67 $R = Piv$

68 $R_1 = R_2 = H$
69 $R_1 + R_2 = -S(O)-$

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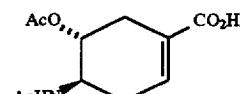
Scheme 7c

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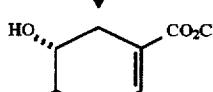
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74



78 $R = N_3$
79 $R = NH_2$

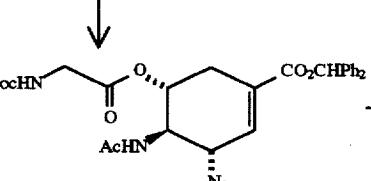
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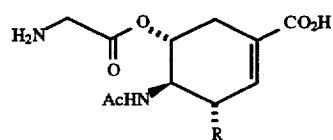
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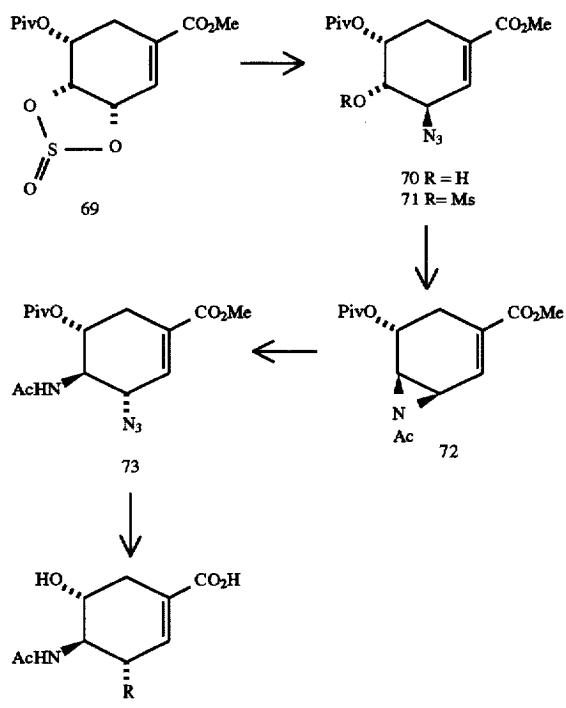
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81 $R = N_3$
82 $R = NH_2$

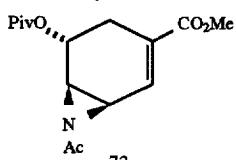
Scheme 7b



69

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$R = H$
 $R = Ms$



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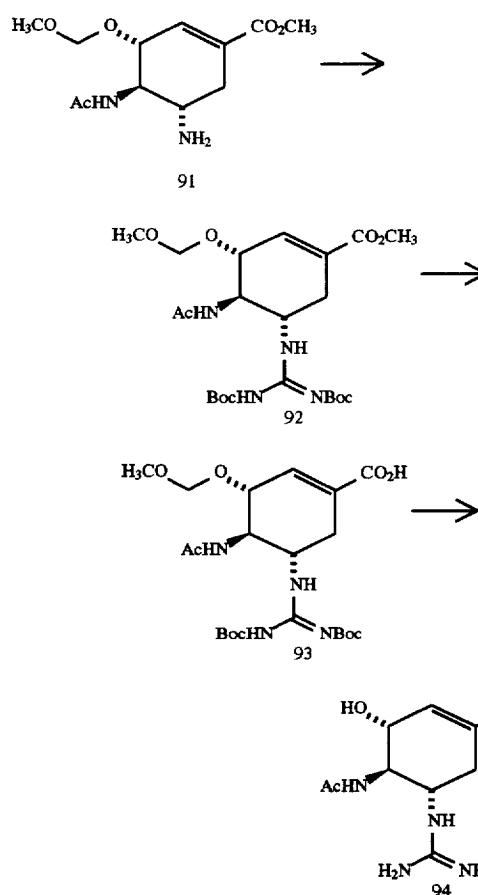
74 $R = N_3$
75 $R = NH_2$

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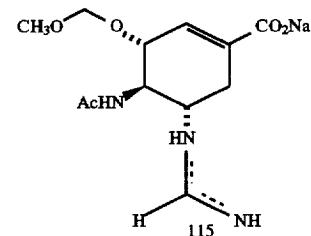
Scheme 8



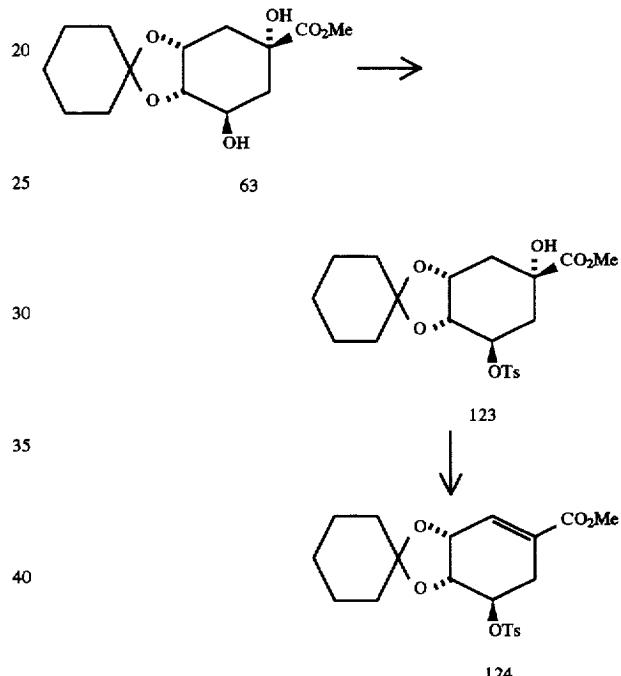
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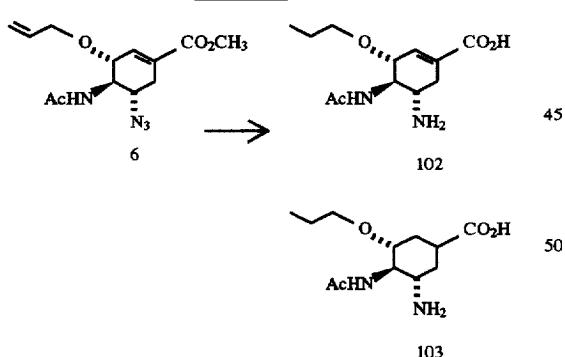
Scheme 10



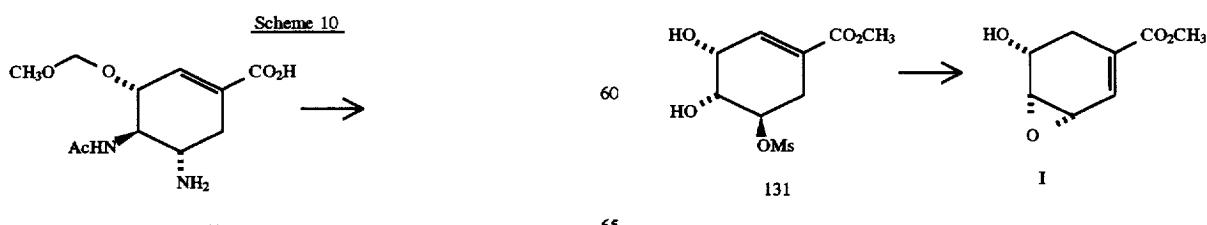
Scheme 11



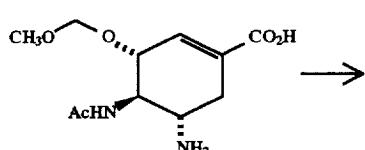
Scheme 9



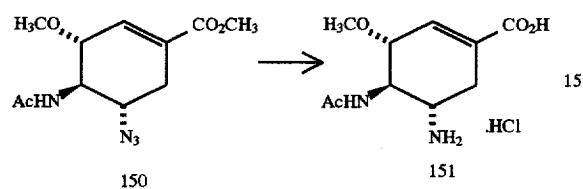
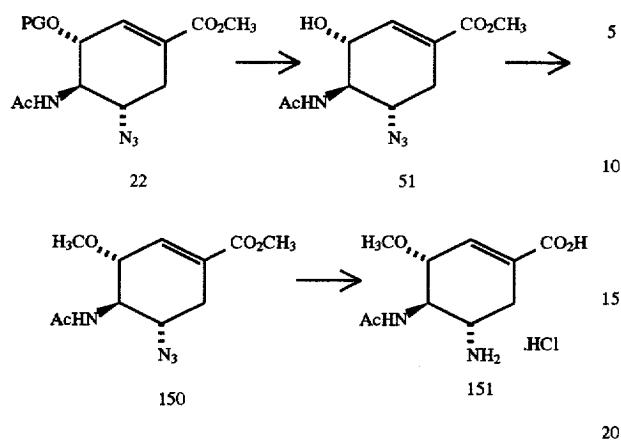
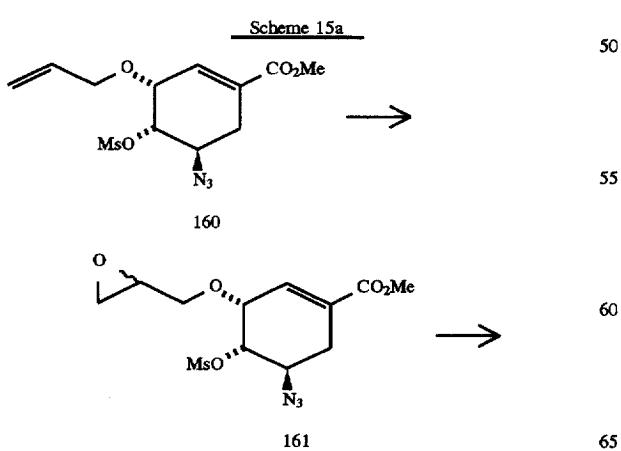
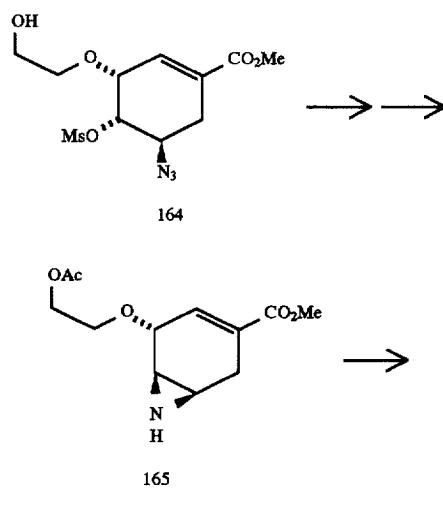
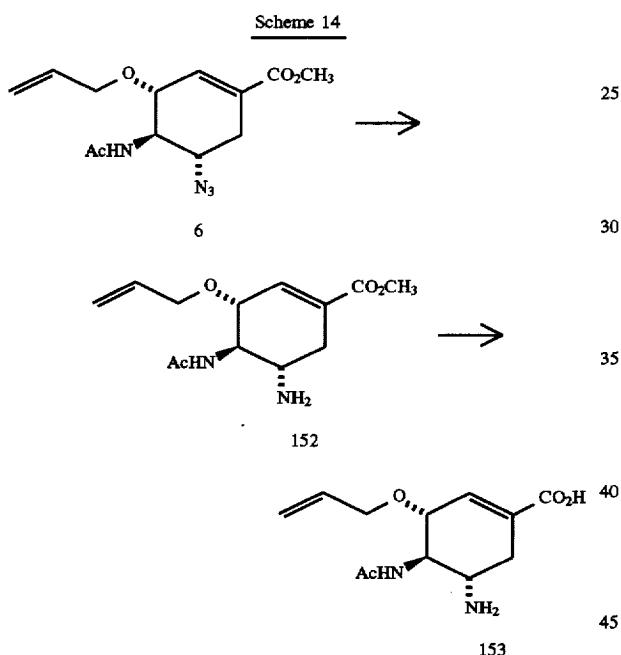
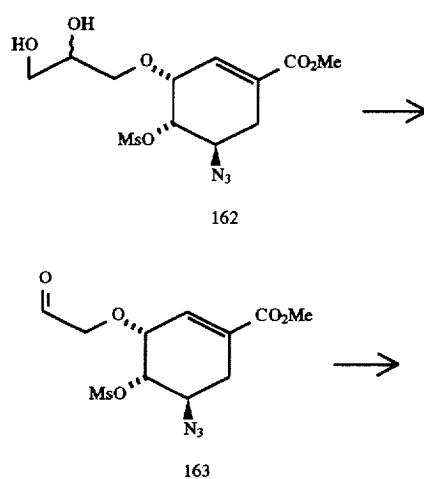
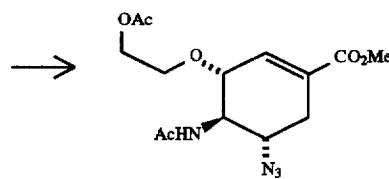
Scheme 12



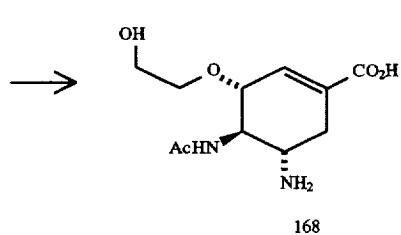
Scheme 10



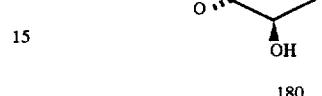
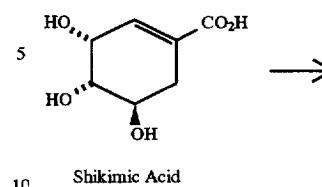
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57Scheme 13**58**-continuedScheme 15aScheme 15b

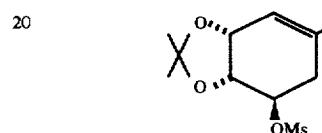
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59-continued
Scheme 15b**60**

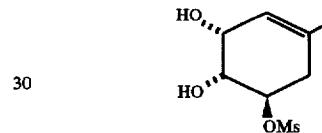
Scheme 17a



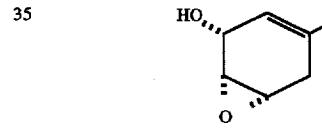
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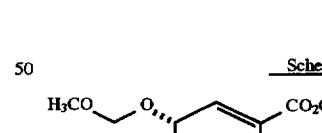
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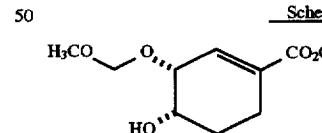


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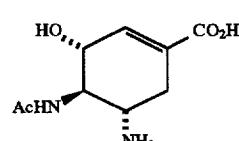
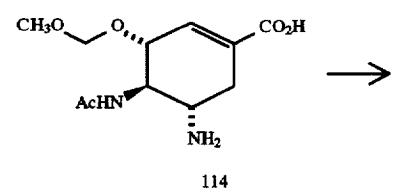
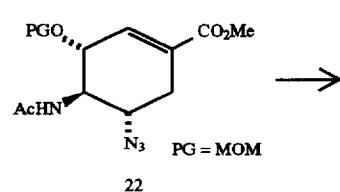
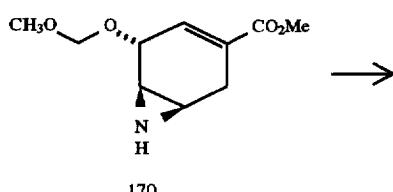


PG = MOM

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PG = MOM



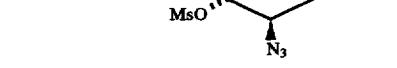
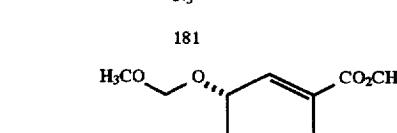
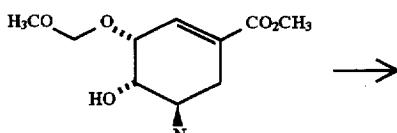
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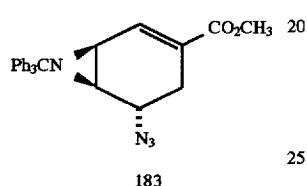
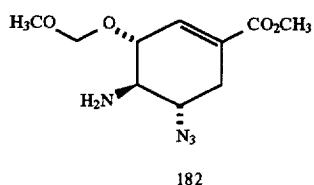
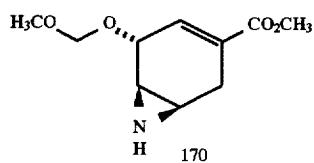
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Scheme 17b

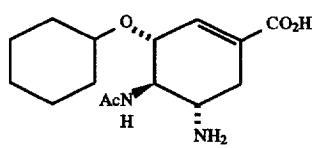
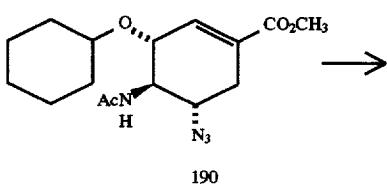
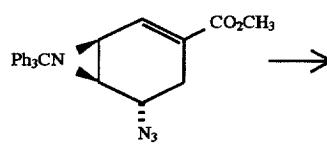


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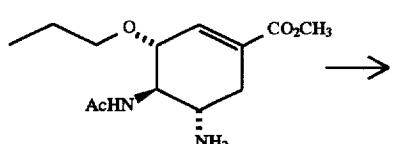
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61-continued
Scheme 17b

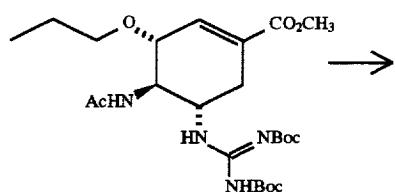
Scheme 18



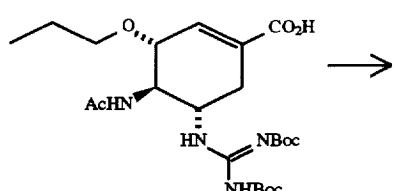
Scheme 19

**62**-continued
Scheme 19

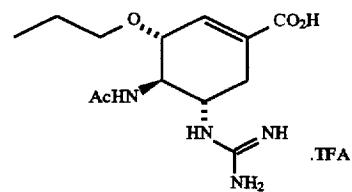
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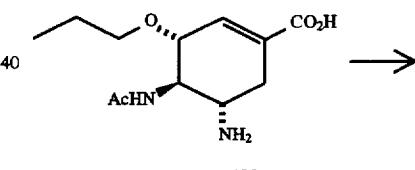
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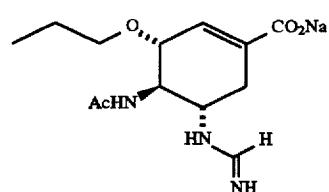
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Scheme 20

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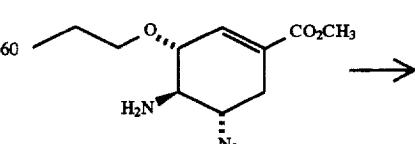
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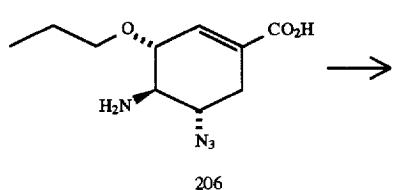
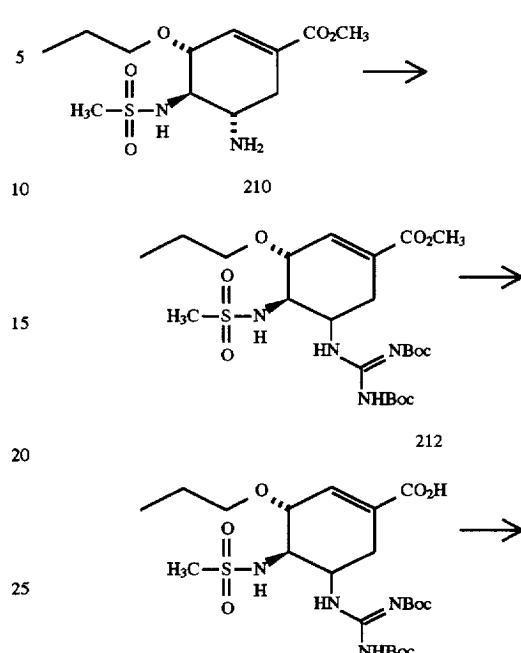
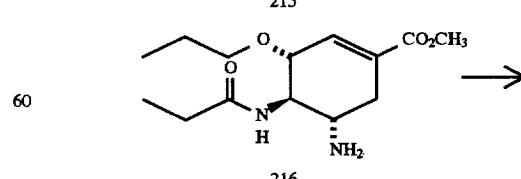
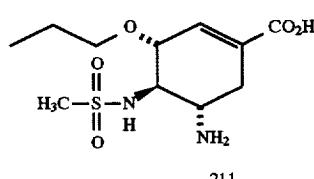
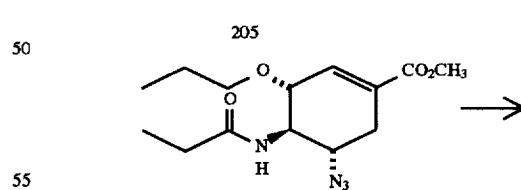
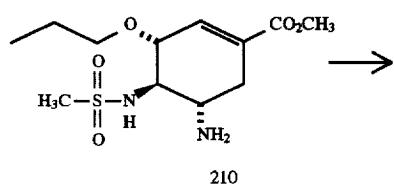
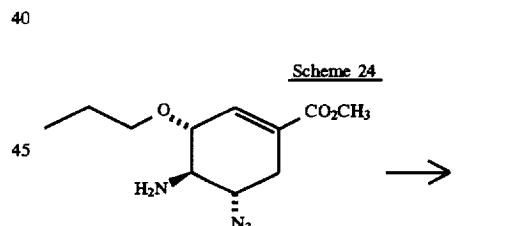
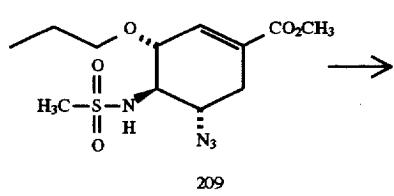
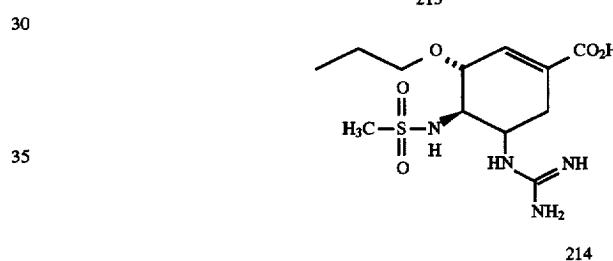
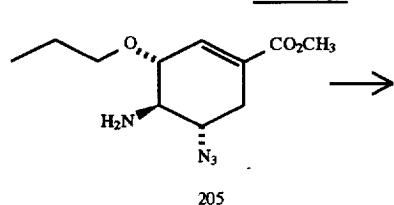
Scheme 21



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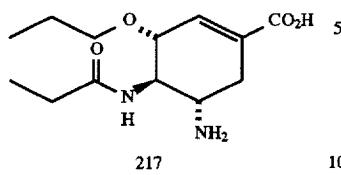
Scheme 21**64**Scheme 23Scheme 22

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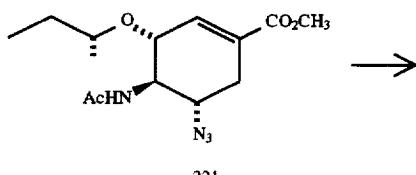
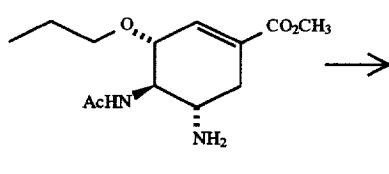
5,763,483

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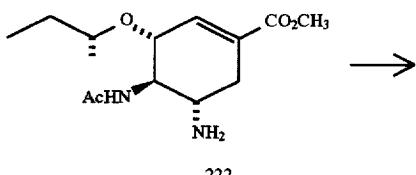
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Scheme 24**66**

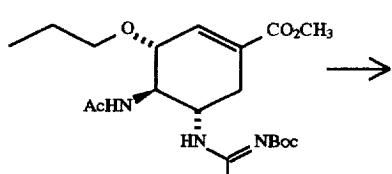
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Scheme 26Scheme 25

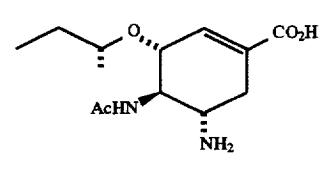
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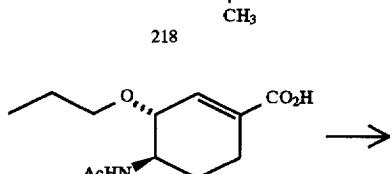
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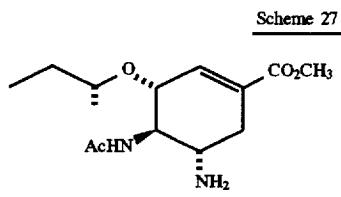
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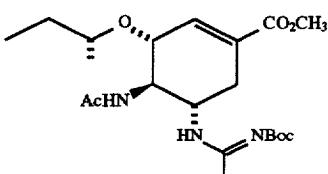
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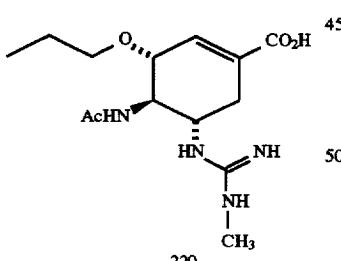
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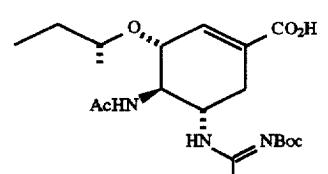
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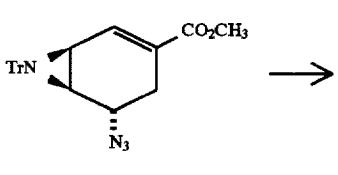
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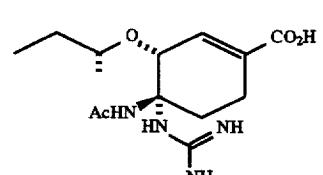
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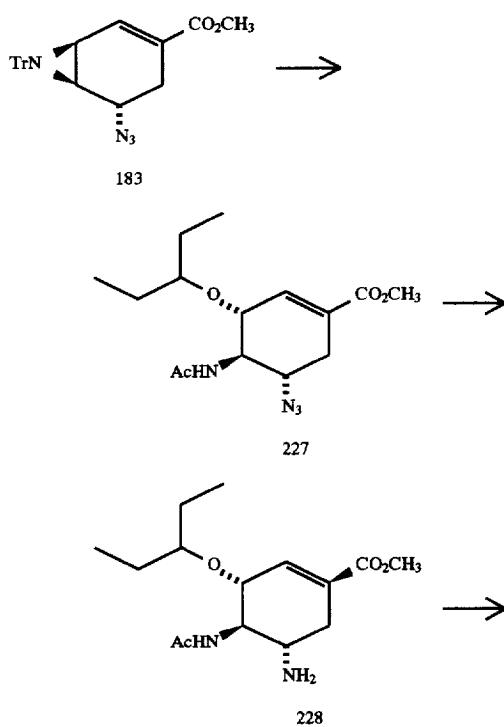
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Scheme 26

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67Scheme 28

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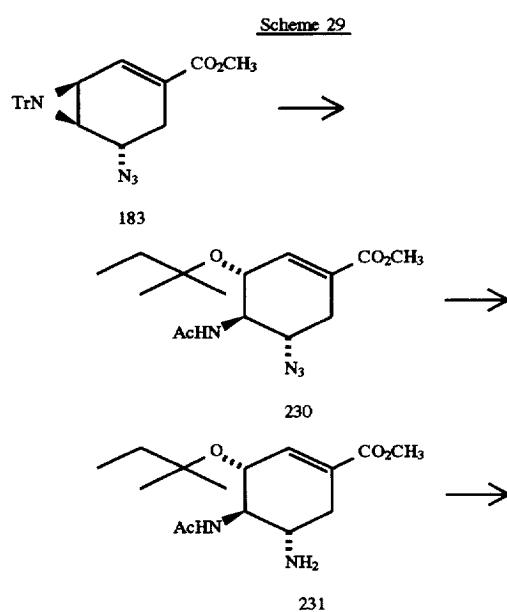
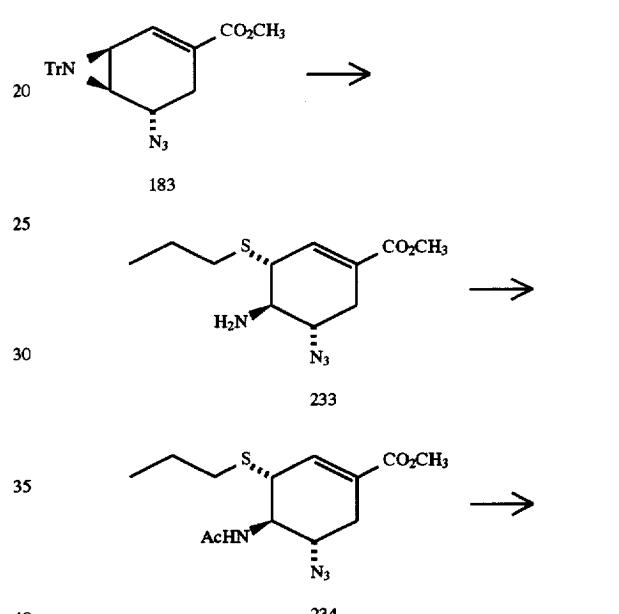
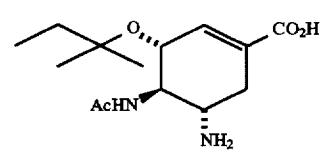
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Scheme 29

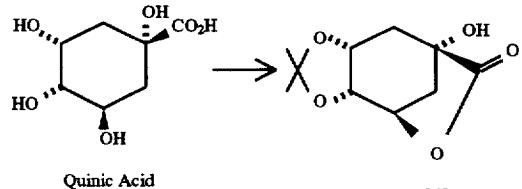
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Scheme 31

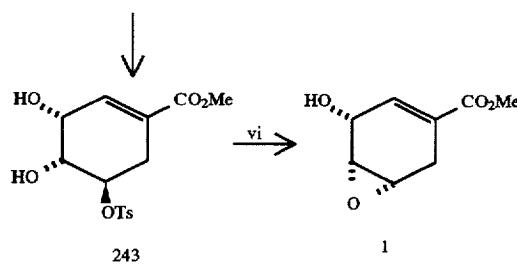
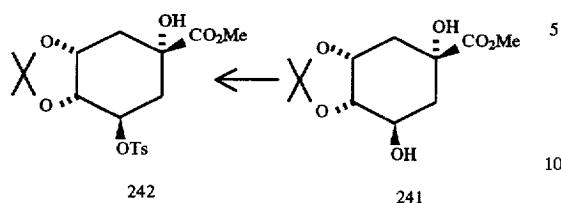
ii

5,763,483

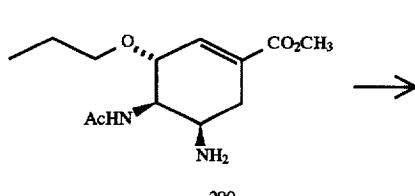
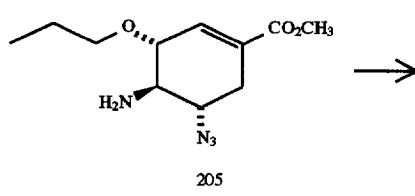
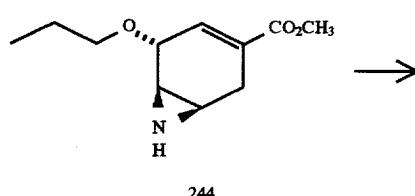
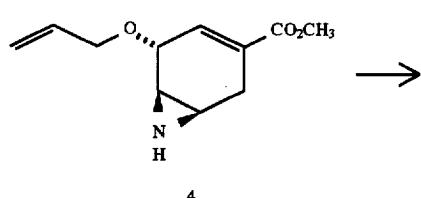
69

-continued

Scheme 31

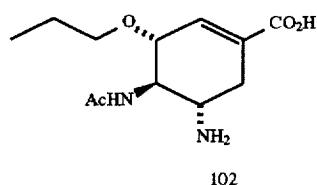


Scheme 32

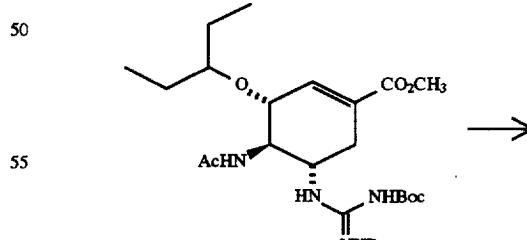
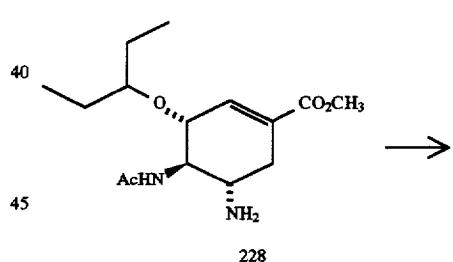
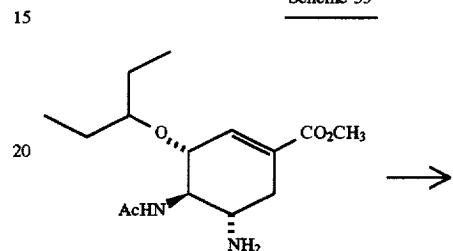
**70**

-continued

Scheme 32



Scheme 33

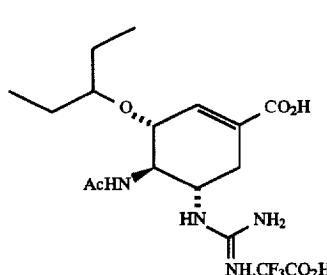


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Scheme 33



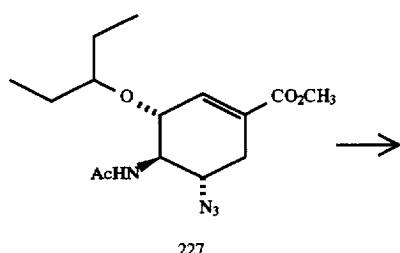
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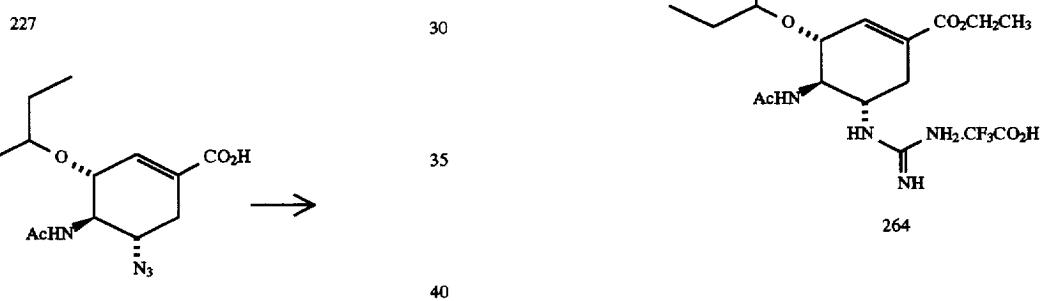
Scheme 34



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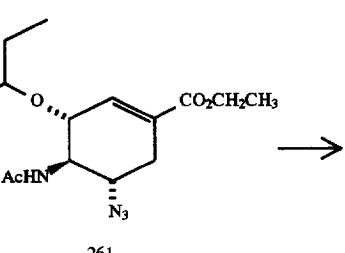
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260

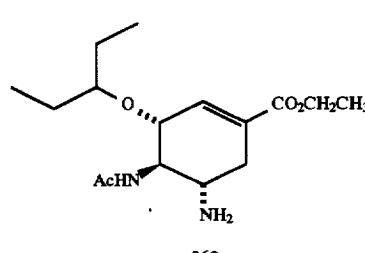
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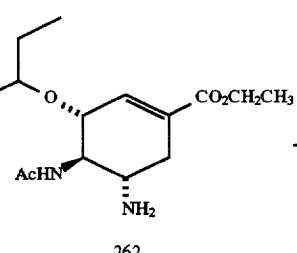
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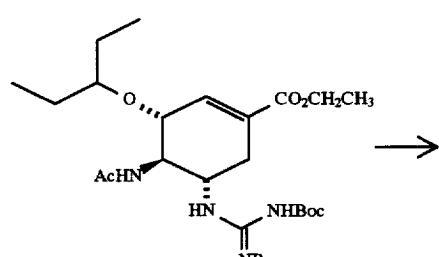
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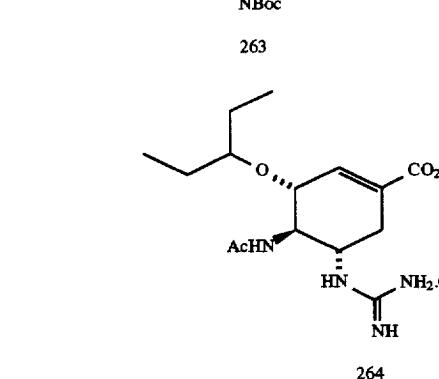
Scheme 35



262

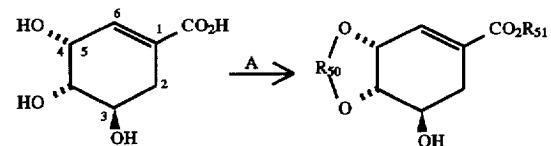


263

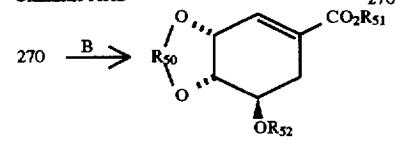


264

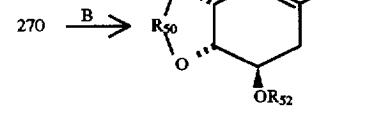
Scheme 36



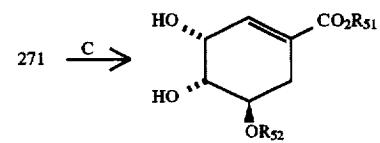
Shikimic Acid



270

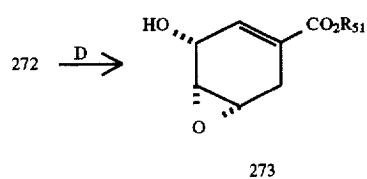
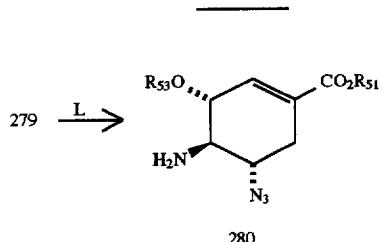
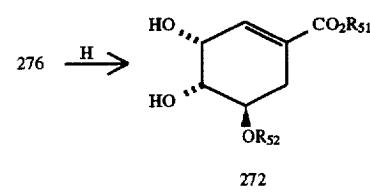
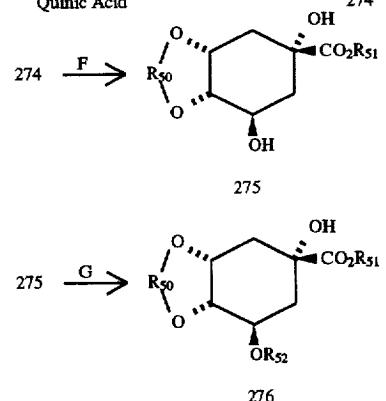
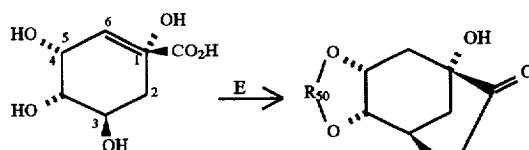
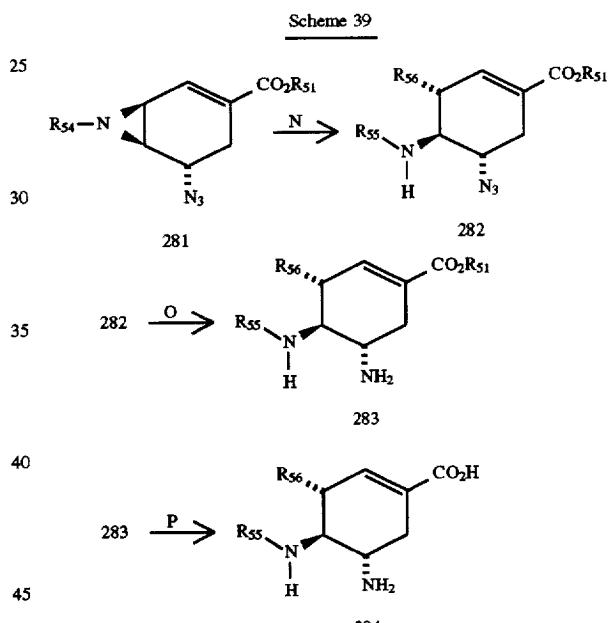
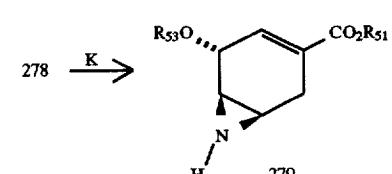
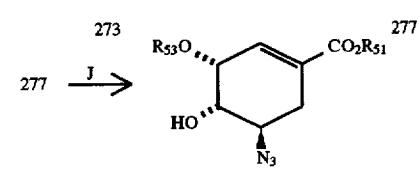
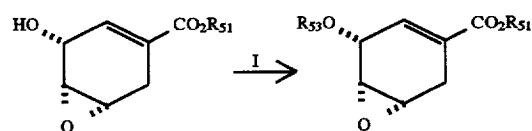
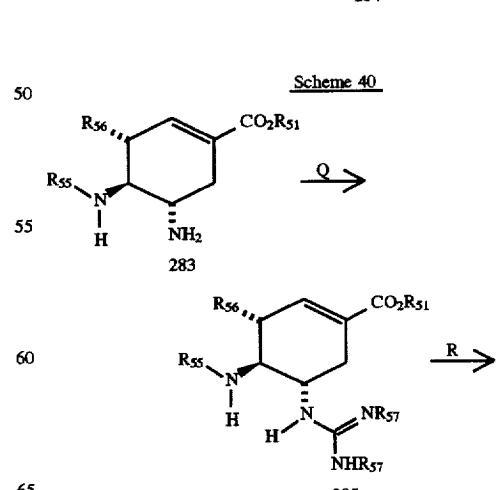


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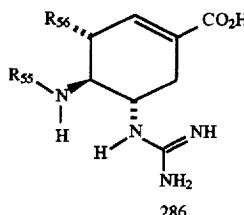
272

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73-continued
Scheme 36**74**-continued
Scheme 38Scheme 37Scheme 38Scheme 39Scheme 40

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-continued
Scheme 40

Additional embodiments of methods of making and using compositions of the invention are depicted in Schemes 36–40. One aspect of the invention is directed to methods of making compounds of the invention comprising processes, A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, or R of Schemes 36–40, alone or in combination with each other. Table 27 describes exemplary method embodiments of processes A–R. Each embodiment is an individual method using the unit processes A–R alone or in combination.

Other aspects of the invention are directed to methods of using shikimic acid to prepare compound 270 shown as A in Schemes 36, methods of using compound 270 to prepare compound 271 shown as B in Schemes 36, methods of using compound 271 to prepare compound 272 shown as C in Schemes 36, methods of using compound 272 to prepare compound 273 shown as D in Schemes 36, methods of using quinic acid to prepare compound 274 shown as E in Schemes 37, methods of using compound 274 to prepare compound 275 shown as F in Schemes 37, methods of using compound 275 to prepare compound 276 shown as G in Schemes 37, methods of using compound 276 to prepare compound 272 shown as H in Schemes 37, methods of using compound 273 to prepare compound 277 shown as I in Schemes 38, methods of using compound 277 to prepare compound 278 shown as J in Schemes 38, methods of using compound 278 to prepare compound 279 shown as K in Schemes 38, methods of using compound 279 to prepare compound 280 shown as L in Schemes 38, methods of using compound 280 to prepare compound 281 shown as M in Schemes 38, methods of using compound 281 to prepare compound 282 shown as N in Schemes 39, methods of using compound 282 to prepare compound 283 shown as O in Schemes 39, methods of using compound 283 to prepare compound 284 shown as P in Schemes 39, methods of using compound 283 to prepare compound 285 shown as Q in Schemes 40, and methods of using compound 285 to prepare compound 286 shown as R in Schemes 40.

General aspects of these exemplary methods are described below and in the Example. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

The terms “treated”, “treating”, “treatment”, and the like, mean contacting, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that “treating compound one with compound two” is synonymous with “allowing compound one to react with compound two”, “contacting compound one with compound two”, “reacting compound one with compound two”, and other expressions common in the art of organic synthesis for reasonably indicating that compound one was “treated”, “reacted”, “allowed to react”, etc., with compound two.

“Treating” indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal

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concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (−100° C. to 250° C. typically −78° C. to 150° C., more typically −78° C. to 100° C., still more typically 0° C. to 100° C.), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for “treating” in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

10 15 Process A. Scheme 36

Shikimic acid is used to prepare compound 270 by the following process.

The cis-4,5-diol function of shikimic acid is differentiated from the carboxylic acid at carbon 1 by selective protection 20 of these two functionalities. Typically the cis-4,5-diol function is protected as a cyclic ketal and the carboxylic acid function is protected as an ester.

R₅₀ is an acid labile 1,2-diol protecting group such as those described in the above incorporated work of Greene, typically a cyclic ketal or acetal, more typically, a ketal of cyclohexanone or acetone. R₅₁ is an acid stable carboxylic acid protecting group such as those described in the above incorporated work of Greene, typically a linear, branched or cyclic alkyl, alkenyl, or alkynyl of 1 to 12 carbon atoms such as those shown as groups 2–7, 9–10, 15, or 100–660 of Table 2, more typically a linear or branched alkyl of 1 to 8 carbon atoms such as those shown as groups 2–5, 9, or 100–358 of Table 2, still more typically a linear or branched alkyl of 1 to 6 carbon atoms such as those shown as groups 2–5, 9, or 100–141 of Table 2, more typically yet, R₅₁ is methyl, ethyl, 30 n-propyl, i-propyl, n-butyl, sec-butyl, i-butyl, or t-butyl.

Shikimic acid is reacted to protect the carboxylic acid with group R₅₁ and the cis-4,5-diol with group R₅₀. Typically shikimic acid is treated with an alcohol, such as methanol, ethanol, n-propanol, or i-propanol, and an acid catalyst, such as a mineral acid or a sulfonic acid such as methane, benzene or toluene sulfonic acid, followed by a dialkyl ketal or acetal of a ketone or aldehyde, such as 40 45 50 55 60 65 2,2-dimethoxy-propane, or 1,1-dimethoxy-cyclohexane, in the presence of the corresponding ketone or aldehyde, such as acetone or cyclohexanone. Optionally, the product of the alcohol and acid catalyst treatment is separated, isolated and/or purified prior to treatment with dialkyl ketal or acetal. Alternatively shikimic acid is treated with CH₂N₂.

Typically, the process comprises treating shikimic acid with an alkanol and a sulfonic acid followed by treating with a geminal-dialkoxyalkane or geminal-dialkoxyalkane and an alkanone or cycloalkanone to form compound 270. More typically, the process comprises treating shikimic acid with an alkanol and a sulfonic acid; evaporating excess alkanol to form a residue; treating the residue with a geminal-dialkoxyalkane or geminal-dialkoxyalkane and an alkanone or cycloalkanone to form compound 270. Still more typically, the process comprises treating shikimic acid with methanol and para-toluenesulfonic acid; evaporating excess methanol to form a residue; treating the residue with 2,2-dimethoxypropane and acetone to form compound 270.

An exemplary embodiment of this process is given as Example 55 below.

65 66 Process B. Scheme 36

Compound 270 is used to prepare compound 271 by the following process.

The hydroxy group at position 3 is activated, typically, activated toward displacement reactions, more typically, activated toward epoxide ring forming displacement with an alcohol at position 4.

R_{52} is an alcohol activating group, typically, an activating group toward displacement reactions, more typically, an activating group toward epoxide ring forming displacement with an alcohol at position 4. Such groups include those typical in the art such as sulfonic acid esters, more typically, methane, benzene or toluene sulfonic acid esters. In one embodiment, R_{52} , taken together with O (i.e. $—OR_{52}$), is a leaving group such as those common in the art.

Typically the process comprises treating compound 270 with an acid halide to form compound 271. More typically, the process comprises treating compound 270 with a sulfonic acid halide in a suitable solvent to form compound 271. Still more typically, the process comprises treating compound 270 with a sulfonic acid halide in a suitable solvent such as an amine, optionally, in the presence of a cosolvent, such as a haloalkane, to form compound 271. More typically yet, the process comprises treating compound 270 with methane sulfonyl chloride in triethylamine/dichloromethane to form compound 271.

An exemplary embodiment of this process is given as Example 56 below.

Process C, Scheme 36

Compound 271 is used to prepare compound 272 by the following process.

The acid labile protecting group (R_{50}) for the hydroxy groups at positions 4 and 5 is removed. Typically, R_{50} is removed without substantially removing base labile carboxylic acid protecting groups (e.g. R_{51}) or hydroxy activating groups (e.g. R_{52}). Still more typically, R_{50} is cleaved under acidic conditions.

Typically the process comprises treating compound 271 with a protic solvent, more typically, in the presence of an acid catalyst as described above. Still more typically, the process comprises treating compound 271 with an alkanol as described above and an acid catalyst as described above. More typically yet, the process comprises treating compound 271 with methanol and para-toluene sulfonic acid to produce compound 272.

An exemplary embodiment of this process is given as Example 57 below.

Process D, Scheme 36

Compound 272 is used to prepare compound 273 by the following process.

The activated hydroxy group at position 3 of compound 272 is displaced by the hydroxy at position 4 of compound 272 to produce epoxide compound 273. Typically the displacement is catalyzed by a suitable base, more typically, an amine base such as DBU or DBN.

Typically the process comprises treating compound 272 with a basic catalyst, optionally in the presence of a suitable solvent. Still more typically, the process comprises treating compound 272 with an amine base in a polar, non-protic solvent such as diethyl ether or THF. More typically yet, the process comprises treating compound 272 with DBU in THF to produce compound 273.

An exemplary embodiment of this process is given as Example 58 below.

Process E, Scheme 37

Quinic acid is used to prepare compound 274 by the following process.

The cis-4,5-diol function of quinic acid is differentiated from the carboxylic acid at carbon 1 by selective protection of these two functionalities. Typically the cis-4,5-diol func-

tion is protected as a cyclic ketal and the carboxylic acid function is protected as a lactone with the hydroxy group at position 3.

R_{50} is as described above.

Typically, the process comprises treating quinic acid with a geminal-dialkoxyalkane or geminal dialkoxyalkane, as described above, and an alkanone or cycloalkanone, as described above, optionally, in the presence of an acid catalyst, as described above, to form compound 274. More typically, the process comprises treating quinic acid with a geminal-dialkoxyalkane or geminal-dialkoxyalkane, an alkanone or cycloalkanone, and an acid catalyst to form compound 270. Still more typically, the process comprises treating quinic acid with 2,2-dimethoxypropane, acetone, and para-toluenesulfonic acid to form compound 274.

An exemplary embodiment of this process is given as Example 101 below.

Process F, Scheme 37

Compound 274 is used to prepare compound 275 by the following process.

The lactone is opened to form compound 275. Typically, the lactone is opened to produce a protected carboxylic acid at position 1 and a free hydroxy at position 3. More typically, the lactone is opened under basic conditions to produce an R_{51} protected carboxylic acid at position 1 and a free hydroxy group at position 3.

R_{51} is as described above.

Typically compound 274 is treated with a suitable base in a suitable protic solvent. More typically compound 275 is treated with a metal hydroxide base, such as sodium, potassium or lithium hydroxide, in an alkanol, as described above. Still more typically, compound 274 is treated with NaOH in MeOH to produce compound 275.

An exemplary embodiment of this process is given as Example 102 below.

Process G, Scheme 37

Compound 275 is used to prepare compound 276 by the following process.

The hydroxy group at position 3 is activated, typically, activated toward displacement reactions, more typically, activated toward epoxide ring forming displacement with an alcohol at position 4.

R_{52} is an alcohol activating group, typically, an activating group toward displacement reactions, more typically, an activating group toward epoxide ring forming displacement with an alcohol at position 4. Such groups include those typical in the art such as sulfonic acid esters, more typically, methane, benzene or toluene sulfonic acid esters. In one embodiment, R_{52} , taken together with O (i.e. $—OR_{52}$), is a leaving group such as those common in the art.

Typically the process comprises treating compound 275 with an acid halide to form compound 276. More typically, the process comprises treating compound 275 with a sulfonic acid halide in a suitable solvent to form compound 276. Still more typically, the process comprises treating compound 275 with a sulfonic acid halide in a suitable solvent such as an amine, optionally, in the presence of a cosolvent, such as a haloalkane, to form compound 276. More typically yet, the process comprises treating compound 275 with methane sulfonyl chloride in triethylamine/dichloromethane to form compound 276.

An exemplary embodiment of this process is given as Example 103 below.

Process H, Scheme 37

Compound 276 is used to prepare compound 272 by the following process.

The hydroxy group at position 1 is eliminated and the cis-4,5-diol protecting group is removed. The hydroxy group

at position 1 is eliminated to form an olefinic bond between positions 1 and 6 and the cis-4,5-diol protecting group is removed to regenerate the cis-4,5-diol.

Typically the process comprises treating compound 276 with a suitable dehydrating agent, such as a mineral acid (HCl, H₂SO₄) or SO₂Cl₂. More typically, compound 276 is treated with SO₂Cl₂, followed by an alkanol, optionally in the presence of an acid catalyst. Still more typically, compound 276 is treated with SO₂Cl₂ in a suitable polar, aprotic solvent, such as an amine to form an olefin; the olefin is treated with an alkanol, as described above, and an acid catalyst, as described above, to form compound 272. More typically yet, compound 276 is treated with SO₂Cl₂ in pyridine/CH₂Cl₂ at a temperature between -100° C. and 0° C., typically -100° C. and -10° C., more typically -78° C., to form an olefin; the olefin is treated with methanol and para-toluene sulfonic acid to form compound 272.

An exemplary embodiment of this process is given as Example 104 below.

Process I, Scheme 38

Compound 273 is used to prepare compound 277 by the following process.

The hydroxy group at position 5 is protected. Typically the protecting group is an acid labile hydroxy protecting. More typically, the protecting group resists transfer to adjacent hydroxy groups.

R₅₃ is an acid labile hydroxy protecting group such as those described in the above incorporated work of Greene. More typically, R₅₃ is an acid cleavable ether, still more typically, R₅₃ is methoxymethyl (MOM, CH₃-O-CH₂-).

Typically the process comprises treating compound 273 with a hydroxy protecting group reagent as described in Greene. More typically the process comprises treating compound 273 with a substituted or unsubstituted haloalkane or alkene, such as methoxymethyl chloride (MOM chloride, CH₃-O-CH₂-Cl), in a suitable solvent, such as a polar, aprotic solvent. Still more typically, the process comprises treating compound 273 with MOM chloride in an amine solvent. More typically yet, the process comprises treating compound 273 with MOM chloride in diisopropyl ethyl amine.

An exemplary embodiment of this process is given as Example 59 below.

Process J, Scheme 38

Compound 277 is used to prepare compound 278 by the following process.

The epoxide at positions 3 and 4 is opened to form an azide. More typically, the epoxide at positions 3 and 4 is opened to form a 3-azido-4-hydroxy compound 278.

Typically the process comprises treating compound 277 with an azide salt in a suitable solvent. More typically, the process comprises treating compound 277 with sodium azide and a mild base, such as an ammonium halide, in a polar, protic solvent, such as an alkanol or water. Still more typically, the process comprises treating compound 277 with sodium azide and ammonium chloride in water/methanol solution to produce compound 278.

An exemplary embodiment of this process is given as Example 60 below.

Process K, Scheme 38

Compound 278 is used to prepare compound 279 by the following process.

The hydroxy group at position 4 of compound 278 is displaced by the 3-azido group to form the aziridine compound 279.

Typically the process comprises treating compound 278 with a hydroxy activating group as described above, an

organophosphine and a base. More typically the process comprises treating compound 278 with a sulfonic acid halide, such as those described above, to form an activated hydroxy compound, treating the activated hydroxy compound with trialkyl or tri arylphosphine, such as triphenylphosphine, to form a phosphonium salt, and treating the phosphonium salt with a base, such as an amine, to form compound 279. Still more typically, the process comprises treating compound 278 with mesyl chloride, to form an activated hydroxy compound, treating the activated hydroxy compound with triphenylphosphine, to form a phosphonium salt, and treating the phosphonium salt with triethylamine and H₂O, to form compound 279.

An exemplary embodiment of this process is given as Examples 61 and 62 below.

Process L, Scheme 38

Compound 279 is used to prepare compound 280 by the following process.

The aziridine compound 279 is opened with azide to form azido amine 280.

Typically the process comprises treating compound 279 with an azide salt in a suitable solvent. More typically, the process comprises treating compound 279 with sodium azide and a mild base, such as an ammonium halide, in a polar, aprotic solvent, such as an ether, amine, or amide. Still more typically, the process comprises treating compound 279 with sodium azide and ammonium chloride in DMF solution to produce compound 280.

An exemplary embodiment of this process is given as Example 63 below.

Process M, Scheme 38

Compound 280 is used to prepare compound 281 by the following process.

The protected hydroxy group at position 5 is displaced by the amine at position 4 to form aziridine 281. Typically the aziridine 281 is substituted with an acid labile group, more typically an aziridine activating group.

R₅₄ is an acid labile group, typically an acid labile amine protecting group such as those described in the above incorporated work of Greene. More typically, R₅₄ is an aziridine activating group, still more typically, a group capable of activating an aziridine toward acid catalyzed ring opening. Typical R₅₄ groups include by way of example and not limitation, a linear or branched 1-oxo-alk-1-yl group of 1 to 12 carbons wherein the alkyl portion is a 1 to 11 carbon linear or branched chain alkyl group (such as CH₃(CH₂)_zC(O)-, z is an integer from 0 to 10, i.e. acetyl CH₃C(O)-, etc.), substituted methyl (e.g. triphenylmethyl, Ph₃C—, trityl, Tr), or a carbamate such as BOC or Cbz or a sulfonate (e.g. alkyl sulphonates such as methyl sulphonate). More typical R₅₄ groups include triphenylmethyl and 1-oxo-alk-1-yl groups having 1 to 8, still more typically, 1, 2, 3, 4, 5, or 6, more typically yet, 2 or 3 carbon atoms.

Typically the process comprises treating compound 280 with a deprotecting agent to remove group R₅₃, an R₅₄ producing reagent such as those described in Greene (R₅₄-halide, such as acetylchloride, or Tr-Cl, or R₅₄-O-R₅₄, such as acetic anhydride), and a hydroxy activating group such as those described in process B, Scheme 36. More typically the process comprises treating compound 280 with a polar, protic solvent, optionally in the presence of an acid catalyst as described above, to form a first intermediate; treating the first intermediate with Tr-Cl in a polar, aprotic solvent, such as an amine, to form a second intermediate; and treating the second intermediate with a sulfonic acid halide, such as mesyl chloride or para toluene sulfonyl chloride, in a polar aprotic solvent, such as an amine, to

produce compound 281. Still more typically, the process comprises treating compound 280 with methanol and HCl, to form a first intermediate; treating the first intermediate with $\text{Tr}-\text{Cl}$ and triethylamine, to form a second intermediate; and treating the second intermediate with mesyl chloride and triethylamine, to produce compound 281.

An exemplary embodiment of this process is given as Example 64 below.

Process N, Scheme 39

Compound 281 is used to prepare compound 282 by the following process.

Aziridine 281 is opened and the resulting amine is substituted with an R_{55} group to form compound 282. Typically, aziridine 281 is opened by acid catalyzed ring opening and the resulting amine is acylated.

R_{55} is W_3 as defined above. Typically R_{55} is $-\text{C}(\text{O})\text{R}_5$.

R_{56} is U_1 as described above. Typically R_{56} is $\text{W}_6-\text{O}-$, $\text{W}_6-\text{S}-$, or $\text{W}_6-\text{N}(\text{H})-$. More typically, R_{56} is $\text{R}_5-\text{O}-$, $\text{R}_5-\text{S}-$, or $\text{R}_5-\text{N}(\text{H})-$.

Typically the process comprises treating compound 281 with an acid catalyst and a compound of the formula $\text{R}_{56}-\text{X}_1-\text{H}$, wherein X_1 is as defined above to form an amine intermediate; and treating the amine intermediate with a compound of the formula $\text{W}_3-\text{O}-\text{W}_3$, W_3-X_{10} , wherein X_{10} is a leaving group, to form compound 282. The acid catalyst is typically a Lewis acid catalyst common in the art, such as $\text{BF}_3\text{Et}_2\text{O}$, TiCl_3 , TMSOTf , $\text{SmI}_2(\text{THF})_2$, LiClO_4 , $\text{Mg}(\text{ClO}_4)_2$, $\text{Ln}(\text{OTf})_3$ (where $\text{Ln}=\text{Yb}$, Gd , Nd), $\text{Ti}(\text{O}-\text{Pr})_4$, AlCl_3 , AlBr_3 , BeCl_2 , CdCl_2 , ZnCl_2 , BF_3 , BCl_3 , BBr_3 , GaCl_3 , GaBr_3 , TiCl_4 , TiBr_4 , ZrCl_4 , SnCl_4 , SnBr_4 , SbCl_5 , SbBr_5 , BiCl_3 , FeCl_3 , UCl_4 , ScCl_3 , YCl_3 , LaCl_3 , CeCl_3 , PrCl_3 , NdCl_3 , SmCl_3 , EuCl_3 , GdCl_3 , TbCl_3 , LuCl_3 , DyCl_3 , HoCl_3 , ErCl_3 , TmCl_3 , YbCl_3 , ZnI_2 , $\text{Al}(\text{OPr})_3$, $\text{Al}(\text{acac})_3$, ZnBr_2 , for SnCl_4 . X_1 is typically $-\text{O}-$, $-\text{S}-$, or $-\text{N}(\text{H})-$. X_{10} is typically a halide such as Cl , Br , or I . More typically, the process comprises treating compound 281 with a compound of the formula R_5-OH , R_5-SH , or R_5-NH_2 , and $\text{BF}_3\text{Et}_2\text{O}$ to form an intermediate; and treating the intermediate with an alkanoic acid anhydride to form compound 282. Still more typically, the process comprises treating compound 281 with a compound of the formula R_5-OH and $\text{BF}_3\text{Et}_2\text{O}$ to form an intermediate; and treating the intermediate with an acetic anhydride to form compound 282. Exemplary compounds of the formula R_5-OH include those described by Table 2, groups 2-7, 9-10, 15, and 100-660 wherein Q_1 is $-\text{OH}$. Further exemplary compounds of the formula R_5-OH include those shown in Table 25 below (together with their Chemical Abstracts Service Registry Numbers) and those shown in Table 26 below (together with their Chemical Abstracts Service Registry Numbers, and Aldrich Chemical Company Product Numbers). More typical exemplary compounds of the formula R_5-OH are those described by Table 2, groups 2-5, 9, and 100-141 wherein Q_1 is $-\text{OH}$.

In another embodiment of Process N, Scheme 39, R_{55} is H .

Typically this process embodiment comprises treating compound 281 with an acid catalyst and a compound of the formula $\text{R}_{56}-\text{X}_1-\text{H}$, wherein X_1 is as defined above to form an amine intermediate to form compound 282. The acid catalyst and X_1 are as described above. More typically, the process comprises treating compound 281 with a compound of the formula R_5-OH , R_5-SH , or R_5-NH_2 , and $\text{BF}_3\text{Et}_2\text{O}$ to form compound 282. Still more typically, the process comprises treating compound 281 with a compound of the formula R_5-OH and $\text{BF}_3\text{Et}_2\text{O}$ to form compound 282. Exemplary compounds of the formula R_5-OH are described above.

Exemplary embodiments of this process are given as Examples 65, 86, 92, and 95 below.

Process O, Scheme 39

Compound 282 is used to prepare compound 283 by the following process.

The azide of compound 282 is reduced to form amino compound 283.

Typically the process comprises treating compound 282 with a reducing agent to form compound 283. More typically the process comprises treating compound 282 with hydrogen gas and a catalyst (such as platinum on carbon or Lindlar's catalyst), or reducing reagents (such as a trialkyl or triaryl phosphine as described above). More typically still, the process comprises treating compound 282 with triphenylphosphine in water/THF to form compound 283.

Exemplary embodiments of this process are given as Examples 87, 93, and 96 below.

Process P, Scheme 39

Compound 283 is used to prepare compound 284 by the following process.

The carboxylic acid protecting group is removed.

Typically the process comprises treating compound 283 with a base. More typically, the process comprises treating compound 283 with a metal hydroxide in a suitable solvent such as an aprotic, polar solvent. More typically still, the process comprises treating compound 283 with aqueous potassium hydroxide in THF to produce compound 284.

Exemplary embodiments of this process are given as Examples 88, 94, and 97 below.

Process Q, Scheme 40

Compound 283 is used to prepare compound 285 by the following process.

The amine is converted to a protected guanidine.

R_{57} is a guanidine protecting group common in the art, such as BOC or Me.

Typically the process comprises treating compound 283 with a guanidylating reagent such as those common in the art. Exemplary reagents include Bis-BOC Thio-Urea aminoinomethanesulfonic acid (Kim; et al.; *Tet. Lett.* 1988, 29(26), 3183-3186) and 1-guanylpyrazoles (Bernatowicz; et al.; *Tet. Lett.* 1993, 34(21), 3389-3392). More typically, the process comprises treating compound 283 with Bis-BOC Thio-Urea acid. Still more typically, the process comprises treating compound 283 with Bis-BOC Thio-Urea acid and HgCl_2 to form compound 285.

An exemplary embodiment of this process is given as Example 67 below.

Process R, Scheme 40

Compound 285 is used to prepare compound 286 by the following process.

The carboxylic acid and guanidine protecting groups are removed.

Typically the process comprises treating compound 285 with a base; followed by treating with an acid, as described above. More typically the process comprises treating compound 285 with a metal hydroxide base, described above, to form an intermediate; and treating the intermediate with acid to form compound 286. Still more typically the process comprises treating compound 285 with aqueous potassium hydroxide and THF, to form an intermediate; and treating the intermediate with TFA to form compound 286.

Exemplary embodiments of this process are given as Examples 68 and 69 below.

TABLE 25

Exemplary Compounds of Formula R ₅ -OH (CAS No.)	
<u>C4 Fluoro Alcohols</u>	5
(R*,R*)-(±)-3-fluoro-2-Butanol (139755-61-6)	
1-fluoro-2-Butanol (124536-12-5)	
(R)-3-fluoro-1-Butanol (120406-57-7)	
3-fluoro-1-Butanol (19808-95-8)	
4-fluoro-2-Butanol (18804-31-4)	10
(R*,S*)-3-fluoro-2-Butanol (6228-94-0)	
(R*,R*)-3-fluoro-2-Butanol (6133-82-0)	
2-fluoro-1-Butanol (4459-24-9)	
2-fluoro-2-methyl-1-Propanol (3109-99-7)	
3-fluoro-2-Butanol (1813-13-4)	
4-fluoro-1-Butanol (372-93-0)	15
1-fluoro-2-methyl-2-Propanol (353-80-0)	
<u>C5 Fluoro Alcohols</u>	
2-fluoro-1-Pentanol (123650-81-7)	
(R)-2-fluoro-3-methyl-1-Butanol (113943-11-6)	
(S)-2-fluoro-3-methyl-1-Butanol (113942-98-6)	
4-fluoro-3-methyl-1-Butanol (104715-25-5)	20
1-fluoro-3-Pentanol (30390-84-2)	
4-fluoro-2-Pentanol (19808-94-7)	
5-fluoro-2-Pentanol (18804-35-8)	
3-fluoro-2-methyl-2-Butanol (7284-96-0)	
2-fluoro-2-methyl-1-Butanol (4456-02-4)	
3-fluoro-3-methyl-2-Butanol (1998-77-2)	
5-fluoro-1-Pentanol (592-80-3)	
<u>C6 Fluoro Alcohols</u>	
(R*(R*,S*))-2-fluoro-3-methyl-1-Pentanol (168749-88-0)	
1-fluoro-2,3-dimethyl-2-Butanol (161082-90-2)	
2-fluoro-2,3-dimethyl-1-Butanol (161082-89-9)	
(R)-2-fluoro-4-methyl-1-Pentanol (157988-30-2)	30
(S*,R*)-2-fluoro-3-methyl-1-Pentanol (151717-18-9)	
(R*,S*)-2-fluoro-3-methyl-1-Pentanol (151657-14-6)	
(S)-2-fluoro-3,3-dimethyl-1-Butanol (141022-94-8)	
(M)-2-fluoro-2-methyl-1-Pentanol (137505-57-8)	
(S)-2-fluoro-1-Hexanol (127608-47-3)	35
3-fluoro-3-methyl-1-Pentanol (112754-22-0)	
3-fluoro-2-methyl-2-Pentanol (69429-54-5)	
2-fluoro-2-methyl-3-Pentanol (69429-53-4)	
1-fluoro-3-Hexanol (30390-85-3)	
5-fluoro-2-methyl-2-Pentanol (21871-78-3)	40
5-fluoro-3-Hexanol (19808-92-5)	
4-fluoro-3-methyl-2-Pentanol (19808-90-3)	
4-fluoro-4-methyl-2-Pentanol (19031-69-7)	
1-fluoro-3,3-dimethyl-2-Butanol (4604-66-4)	
2-fluoro-2-methyl-1-Pentanol (4456-03-5)	
2-fluoro-4-methyl-1-Pentanol (4455-95-2)	
2-fluoro-1-Hexanol (1786-48-7)	45
3-fluoro-2,3-dimethyl-2-Butanol (661-63-2)	
6-fluoro-1-Hexanol (373-32-0)	
<u>C7 Fluoro Alcohols</u>	
5-fluoro-5-methyl-1-Hexanol (168268-63-1)	
(R)-1-fluoro-2-methyl-2-Hexanol (153683-63-7)	
(S)-3-fluoro-1-Heptanol (141716-56-5)	
(S)-2-fluoro-2-methyl-1-Hexanol (132354-09-7)	50
(R)-3-fluoro-1-Heptanol (120406-54-4)	
(S)-2-fluoro-1-Heptanol (110500-31-7)	
1-fluoro-3-Heptanol (30390-86-4)	
7-fluoro-2-Heptanol (18804-38-1)	
2-ethyl-2-(fluoromethyl)-1-Butanol (14800-35-2)	55
2-(fluoromethyl)-2-methyl-1-Pentanol (13674-80-1)	
2-fluoro-5-methyl-1-Hexanol (4455-97-4)	
2-fluoro-1-Heptanol (1786-49-8)	
7-fluoro-1-Heptanol (408-16-2)	
<u>C8 Fluoro Alcohols</u>	
(M)-2-fluoro-2-methyl-1-Heptanol (137505-55-6)	
6-fluoro-6-methyl-1-Heptanol (135124-57-1)	
1-fluoro-2-Octanol (127296-11-1)	
(R)-2-fluoro-1-Octanol (118205-91-7)	
(±)-2-fluoro-2-methyl-1-Heptanol (117169-40-1)	
(S)-2-fluoro-1-Octanol (110500-32-8)	60
(S)-1-fluoro-2-Octanol (110270-44-5)	
(R)-1-fluoro-2-Octanol (110270-42-3)	

TABLE 25-continued

Exemplary Compounds of Formula R ₅ -OH (CAS No.)	
<u>C9 Fluoro Alcohols</u>	5
(±)-1-fluoro-2-Octanol (110229-70-4)	
2-fluoro-4-methyl-3-Heptanol (87777-41-1)	
2-fluoro-6-methyl-1-Heptanol (4455-99-6)	
2-fluoro-1-Octanol (4455-93-0)	
8-fluoro-1-Octanol (408-27-5)	
<u>C10 Fluoro Alcohols</u>	10
6-fluoro-2,6-dimethyl-2-Heptanol (160981-64-6)	
(S)-3-fluoro-1-Nonanol (160706-24-1)	
(R,-(R*,R*))-3-fluoro-2-Nonanol (137909-46-7)	
(R,-(R*,S*))-3-fluoro-2-Nonanol (137909-45-6)	
3-fluoro-2-Nonanol (137639-20-4)	
(S-(R*,R*))-3-fluoro-2-Nonanol (137639-19-1)	
(S-(R*,S*))-3-fluoro-2-Nonanol (137639-18-0)	
(±)-3-fluoro-1-Nonanol (134056-76-1)	
2-fluoro-1-Nonanol (123650-79-3)	
2-fluoro-2-methyl-1-Octanol (120400-89-7)	
(R)-2-fluoro-1-Nonanol (118243-18-8)	
(S)-1-fluoro-2-Nonanol (111423-41-7)	
(S)-2-fluoro-1-Nonanol (110500-33-9)	
1-fluoro-3-Nonanol (30390-87-5)	
2-fluoro-2,6-dimethyl-3-Heptanol (684-74-2)	
9-fluoro-1-Nonanol (463-24-1)	
<u>C11 Fluoro Alcohols</u>	15
4-fluoro-1-Decanol (167686-45-5)	
(P)-10-fluoro-3-Decanol (145438-91-1)	
(R,-(R*,R*))-3-fluoro-5-methyl-1-Nonanol (144088-79-9)	
(P)-10-fluoro-2-Decanol (139750-57-5)	
1-fluoro-2-Decanol (130876-22-1)	
(S)-2-fluoro-1-Decanol (127608-48-4)	
(R)-1-fluoro-2-Decanol (119105-16-7)	
(S)-1-fluoro-2-Decanol (119105-15-6)	
2-fluoro-1-Decanol (110500-35-1)	
1-fluoro-5-Decanol (106533-31-7)	
4-fluoro-2,2,5,5-tetramethyl-3-Hexanol (24212-87-1)	
10-fluoro-1-Decanol (334-64-5)	
<u>C12 Fluoro Alcohols</u>	20
10-fluoro-2-methyl-1-Decanol (139750-53-1)	
2-fluoro-1-Undecanol (110500-34-0)	
8-fluoro-5,5-dimethyl-5-Nonanol (110318-90-6)	
11-fluoro-2-Undecanol (101803-63-8)	
11-fluoro-1-Undecanol (463-36-5)	
<u>C13 Fluoro Alcohols</u>	25
11-fluoro-2-methyl-1-Undecanol (139750-52-0)	
1-fluoro-2-Dodecanol (132547-33-2)	
(R*,S*)-7-fluoro-6-Dodecanol (130888-52-7)	
(R*,R*)-7-fluoro-6-Dodecanol (130876-18-5)	
(S)-2-fluoro-1-Dodecanol (127608-49-5)	
12-fluoro-2-pentyl-Heptanol (120400-91-1)	
(R*,S*)-(±)-7-fluoro-6-Dodecanol (119174-39-9)	
(R*,R*)-(±)-7-fluoro-6-Dodecanol (119174-38-8)	
2-fluoro-1-Dodecanol (110500-36-2)	
11-fluoro-2-methyl-2-Undecanol (101803-67-2)	
1-fluoro-1-Dodecanol (100278-87-3)	
12-fluoro-1-Dodecanol (353-31-1)	
<u>C4 Nitro Alcohols</u>	30
(R)-4-nitro-2-Butanol (129520-34-9)	
(S)-4-nitro-2-Butanol (120293-74-5)	
4-nitro-1-Butanol radical ion(1- ⁻) (83051-13-2)	
(R*,S*)-3-nitro-2-Butanol (82978-02-7)	
(R*,R*)-3-nitro-2-Butanol (82978-01-6)	
4-nitro-1-Butanol (75694-90-5)	
(±)-4-nitro-2-Butanol (72959-86-5)	
4-nitro-2-Butanol (55265-82-2),	
1-aci-nitro-2-Butanol (22916-75-2)	
3-aci-nitro-2-Butanol (22916-74-1)	
2-methyl-3-nitro-1-Propanol (21527-52-6)	
3-nitro-2-Butanol (6270-16-2)	
2-methyl-1-nitro-2-Propanol (5447-98-3)	
2-aci-nitro-1-Butanol (4167-97-9)	
1-nitro-2-Butanol (3156-74-9)	
2-nitro-1-Butanol (609-31-4)	
2-methyl-2-nitro-1-Propanol (76-39-1)	
<u>C5 Nitro Alcohols</u>	35
(R)-4-nitro-2-Butanol (129520-34-9)	
(S)-4-nitro-2-Butanol (120293-74-5)	
4-nitro-1-Butanol radical ion(1- ⁻) (83051-13-2)	
(R*,S*)-3-nitro-2-Butanol (82978-02-7)	
(R*,R*)-3-nitro-2-Butanol (82978-01-6)	
4-nitro-1-Butanol (75694-90-5)	
(±)-4-nitro-2-Butanol (72959-86-5)	
4-nitro-2-Butanol (55265-82-2),	
1-aci-nitro-2-Butanol (22916-75-2)	
3-aci-nitro-2-Butanol (22916-74-1)	
2-methyl-3-nitro-1-Propanol (21527-52-6)	
3-nitro-2-Butanol (6270-16-2)	
2-methyl-1-nitro-2-Propanol (5447-98-3)	
2-aci-nitro-1-Butanol (4167-97-9)	
1-nitro-2-Butanol (3156-74-9)	
2-nitro-1-Butanol (609-31-4)	
2-methyl-2-nitro-1-Propanol (76-39-1)	

TABLE 25-continued

Exemplary Compounds of Formula R ₅ -OH (CAS No.)	
C5 Nitro Alcohols	
(R)-3-methyl-3-nitro-2-Butanol (154278-27-0)	5
3-methyl-1-nitro-1-Butanol (153977-20-9)	
(±)-1-nitro-3-Pentanol (144179-64-6)	
(S)-1-nitro-3-Pentanol (144139-35-5)	
(R)-1-nitro-3-Pentanol (144139-34-4)	10
(R)-3-methyl-1-nitro-2-Butanol (141434-98-2)	
(±)-3-methyl-1-nitro-2-Butanol (141377-55-1)	
(R*,R*)-3-nitro-2-Pentanol (138751-72-1)	
(R*,S*)-3-nitro-2-Pentanol (138751-71-0)	
(R*,R*)-2-nitro-3-Pentanol (138668-26-5)	
(R*,S*)-2-nitro-3-Pentanol (138668-19-6)	15
3-nitro-1-Pentanol (135462-98-5)	
(R)-5-nitro-2-Pentanol (129520-35-0)	
(S)-5-nitro-2-Pentanol (120293-75-6)	
4-nitro-1-Pentanol (116435-64-4)	
(±)-3-methyl-3-nitro-2-Butanol (114613-30-8)	
(S)-3-methyl-3-nitro-2-Butanol (109849-50-5)	
3-methyl-4-nitro-2-Butanol (96597-30-7)	20
(±)-5-nitro-2-Pentanol (78174-81-9)	
2-methyl-2-nitro-1-Butanol (77392-55-3)	
3-methyl-2-nitro-1-Butanol (77392-54-2)	
3-methyl-4-nitro-1-Butanol (75694-89-2)	
2-methyl-4-nitro-2-Butanol (72183-50-7)	25
3-methyl-3-nitro-1-Butanol (65102-50-3)	
5-nitro-2-Pentanol (54045-33-9)	
2-methyl-1-aci-nitro-2-Butanol (22916-79-6)	
2-methyl-1-aci-nitro-2-Butanol (22916-78-5)	
2-methyl-3-nitro-2-Butanol (22916-77-4)	
2-methyl-1-nitro-2-Butanol (22916-76-3)	
5-nitro-1-Pentanol (21823-27-8)	30
2-methyl-3-nitro-1-Butanol (21527-53-7)	
2-nitro-3-Pentanol (20575-40-0)	
3-methyl-3-nitro-2-Butanol (20575-38-6)	
3-nitro-2-Pentanol (5447-99-4)	
2-nitro-1-Pentanol (2899-90-3)	35
3-methyl-1-nitro-2-Butanol (2224-38-6)	
1-nitro-2-Pentanol (2224-37-5)	
C6 Nitro Alcohols	
(-)-4-methyl-1-nitro-2-Pentanol (158072-33-4)	
3-(nitromethyl)-3-Pentanol (156544-56-8)	
(R*,R*)-3-methyl-2-nitro-3-Pentanol (148319-17-9)	
(R*,S*)-3-methyl-2-nitro-3-Pentanol (148319-16-8)	40
6-nitro-2-Hexanol (146353-95-9)	
(±)-6-nitro-3-Hexanol (144179-63-5)	
(S)-6-nitro-3-Hexanol (144139-33-3)	
(R)-6-nitro-3-Hexanol (144139-32-2)	
3-nitro-2-Hexanol (127143-52-6)	45
5-nitro-2-Hexanol (110364-37-9)	
4-methyl-1-nitro-2-Pentanol (102014-44-8)	
(R*,S*)-2-methyl-4-nitro-3-Pentanol (82945-29-7)	
(R*,R*)-2-methyl-4-nitro-3-Pentanol (82945-20-8)	
2-methyl-5-nitro-2-Pentanol (79928-61-3)	
2,3-dimethyl-1-nitro-2-Butanol (68454-59-1)	50
2-methyl-3-nitro-2-Pentanol (59906-62-6)	
3,3-dimethyl-1-nitro-2-Butanol (58054-88-9)	
2,3-dimethyl-3-nitro-2-Butanol (51483-61-5)	
2-methyl-1-nitro-2-Pentanol (49746-26-1)	
3,3-dimethyl-2-nitro-1-Butanol (37477-66-0)	
6-nitro-1-Hexanol (31968-54-4)	
2-methyl-3-nitro-1-Pentanol (21527-55-9)	55
2,3-dimethyl-3-nitro-1-Butanol (21527-54-8)	
2-methyl-4-nitro-3-Pentanol (20570-70-1)	
2-methyl-2-nitro-3-Pentanol (20570-67-6)	
2-nitro-3-Hexanol (5448-00-0)	
4-nitro-3-Hexanol (5342-71-2)	60
4-methyl-4-nitro-1-Pentanol (5215-92-9)	
1-nitro-2-Hexanol (2224-40-0)	
C7 Nitro Alcohols	
1-nitro-4-Heptanol (167696-66-4)	
(R)-1-nitro-2-Heptanol (146608-19-7)	
7-nitro-1-Heptanol (133088-94-5)	
(R*,S*)-3-nitro-2-Heptanol (127143-73-1)	
(R*,R*)-3-nitro-2-Heptanol (127143-72-0)	65

TABLE 25-continued

Exemplary Compounds of Formula R ₅ -OH (CAS No.)	
C8 Nitro Alcohols	
(R*,S*)-2-nitro-3-Heptanol (127143-71-9)	5
(R*,R*)-2-nitro-3-Heptanol (127143-70-8)	
(R*,S*)-2-methyl-5-nitro-3-Hexanol (103077-95-8)	
(R*,R*)-2-methyl-5-nitro-3-Hexanol (103077-87-8)	
3-ethyl-4-nitro-1-Pentanol (92454-38-1)	10
3-ethyl-2-nitro-3-Pentanol (77922-54-4)	
2-nitro-3-Heptanol (61097-77-6)	
2-methyl-1-nitro-3-Hexanol (35469-17-1)	
2-methyl-4-nitro-3-Hexanol (20570-71-2)	
2-methyl-2-nitro-3-Hexanol (20570-69-8)	
5-methyl-5-nitro-2-Heptanol (7251-87-8)	
1-nitro-2-Heptanol (6302-74-5)	
3-nitro-4-Heptanol (5462-04-4)	15
4-nitro-3-Heptanol (5342-70-1)	
C8 Nitro Alcohols	
(±)-1-nitro-3-Octanol (141956-93-6)	20
1-nitro-4-Octanol (167642-45-7)	
(S)-1-nitro-4-Octanol (167642-18-4)	
6-methyl-6-nitro-2-Heptanol (142991-77-3)	
(R*,S*)-2-nitro-3-Octanol (135764-74-8)	
(R*,R*)-2-nitro-3-Octanol (135764-73-7)	
5-nitro-4-Octanol (132272-46-9)	
(R*,R*)-3-nitro-4-Octanol (130711-79-4)	
(R*,S*)-3-nitro-4-Octanol (130711-78-3)	
4-ethyl-2-nitro-3-Hexanol (126939-74-0)	25
2-nitro-3-Octanol (126939-73-9)	
1-nitro-3-Octanol (126495-48-5)	
(R*,R*)-(±)-3-nitro-4-Octanol (118869-22-0)	
(R*,S*)-(±)-3-nitro-4-Octanol (118869-21-9)	
3-nitro-2-Octanol (127143-53-7)	
(R*,S*)-2-methyl-5-nitro-3-Heptanol (103078-03-1)	30
(R*,R*)-2-methyl-5-nitro-3-Heptanol (103077-90-3)	
8-nitro-1-Octanol (101972-90-1)	
(±)-2-nitro-1-Octanol (96039-95-1)	
3,4-dimethyl-1-nitro-2-Hexanol (64592-02-5)	
3-(nitromethyl)-4-Heptanol (35469-20-6)	
2,5-dimethyl-1-nitro-3-Hexanol (35469-19-3)	
2-methyl-1-nitro-3-Heptanol (35469-18-2)	
2,4,4-trimethyl-1-nitro-2-Pentanol (35223-67-7)	
2,5-dimethyl-4-nitro-3-Hexanol (22482-65-1)	
2-nitro-1-Octanol (2882-67-9)	
1-nitro-2-Octanol (2224-39-7)	
C9 Nitro Alcohols	
4-nitro-3-Nonanol (160487-89-8)	35
(R*,R*)-3-ethyl-2-nitro-3-Heptanol (148319-18-0)	
2,6-dimethyl-6-nitro-2-Heptanol (117030-50-9)	
(R*,S*)-2-nitro-4-Nonanol (103077-93-6)	
(R*,R*)-2-nitro-4-Nonanol (103077-85-6)	
2-nitro-3-Nonanol (99706-65-7)	
9-nitro-1-Nonanol (81541-84-6)	40
2-methyl-1-nitro-3-Octanol (53711-06-1)	
4-nitro-5-Nonanol (34566-13-7)	
2-methyl-3-(nitromethyl)-3-Heptenol (5582-88-7)	
1-nitro-2-Nonanol (4013-87-0)	
C10 Nitro Alcohols	
2-nitro-4-Decanol (141956-94-7)	45
(R*,S*)-3-nitro-4-Decanol (135764-76-0)	
(R*,R*)-3-nitro-4-Decanol (135764-75-9)	
5,5-dimethyl-4-(2-nitroethyl)-1-Heptanol (133088-96-7)	
(R*,R*)-(±)-3-nitro-4-Decanol (118869-20-8)	
(R*,S*)-(±)-3-nitro-4-Decanol (118869-19-5)	
5-nitro-2-Decanol (112882-29-8)	
3-nitro-4-Decanol (93297-82-6)	
4,6,6-trimethyl-1-nitro-2-Heptanol (85996-72-1)	
2-methyl-2-nitro-3-Nonanol (80379-17-5)	
1-nitro-2-Decanol (65299-35-6)	50
2,2,4,4-tetramethyl-3-(nitromethyl)-3-Pentanol (58293-26-8)	
C11 Nitro Alcohols	
11-nitro-5-Undecanol (167696-69-7)	55
(R*,R*)-2-nitro-3-Undecanol (144434-56-0)	
(R*,S*)-2-nitro-3-Undecanol (144434-55-9)	
2-nitro-3-Undecanol (143464-92-0)	
2,2-dimethyl-4-nitro-3-Nonanol (126939-76-2)	

TABLE 25-continued

Exemplary Compounds of Formula R ₅ -OH (CAS No.)		
4,8-dimethyl-2-nitro-1-Nonanol (118304-30-6)		
11-nitro-1-Undecanol (81541-83-5)		
C12 Nitro Alcohols		
2-methyl-2-nitro-3-Undecanol (126939-75-1)		
2-nitro-1-Dodecanol (62322-32-1)		
1-nitro-2-Dodecanol (62322-31-0)		
2-nitro-3-Dodecanol (82981-40-6)		
12-nitro-1-Dodecanol (81541-78-8)		

TABLE 26

Exemplary Compounds of Formula R ₅ -OH (CAS No./Aldrich No.)		
3-BROMO-1-PROPANOL	627189	167169
1,3-DICHLORO-2-PROPANOL	96231	184489
3-CHLORO-2,2-DIMETHYL-1-PROPANOL	13401564	189316
2,2-BIS(CHLOROMETHYL)-1-PROPANOL	5355544	207691
1,3-DIFLUORO-2-PROPANOL	453134	176923
2-(METHYLTHIO)ETHANOL	5271385	226424
2-(DIBUTYLAMINO)ETHANOL	102818	168491
2-(DIISOPROPYLAMINO)ETHANOL	96800	168726
3-METHYL-3-BUTEN-1-OL	763326	129402
2-METHYL-3-BUTEN-2-OL	115184	136816
3-METHYL-2-BUTEN-1-OL	556821	162353
4-HEXEN-1-OL	928927	237604
5-HEXEN-1-OL	821410	230324
CIS-2-HEXEN-1-OL	928949	224707
TRANS-3-HEXEN-1-OL	928972	224715
TRANS-2-HEXEN-1-OL	928950	132667
(+/-)-6-METHYL-5-HEPTEN-2-OL	4630062	195871
DIHYDROMYRCENOL	18479588	196428
TRANS,TRANS-2,4-HEXADIEN-1-OL	17102646	183059
2,4-DIMETHYL-2,6-HEPTADIEN-1-OL	80192569	238767
GERANIOL	106241	163333
3-BUTYN-1-OL	927742	130850
3-PENTYN-1-OL	10229104	208698
ISETHIONIC ACID, SODIUM SALT	1562001	220078
(4-(2-HYDROXYETHYL)-1-PIPERAZINE-PROPANESULFONIC ACID)	16052065	163740
HEPES, SODIUM SALT	75277393	233889
1-METHYLCYCLOPROPANEMETHANOL	2746147	236594
2-METHYLCYCLOPROPANEMETHANOL	6077721	233811
(+/-)-CHRYSANthemYL ALCOHOL	18383590	194654
CYCLOBUTANEMETHANOL	4415821	187917
3-CYCLOPENTYL-1-PROPANOL	767055	187275
1-ETHYNYL CYCLOPENTANOL	17356193	130869
3-METHYLCYCLOHEXANOL	591231	139734
3,3,5,5-TETRAMETHYLCYCLOHEXANOL	2650400	190624
4-CYCLOHEXYL-1-BUTANOL	4441570	197408
DIHYDROCARVEOL	619012	218421
(1S,2R,5S)-(+)-MENTHOL	15356704	224464
(1S,2S,5R)-(+)-NEOMENTHOL	2216526	235180
(1S,2R,5R)-(+)-ISOMENTHOL	23283978	242195
(+/-)-3-CYCLOHEXENE-1-METHANOL	72581329	162167
(+)-P-MENTH-1-EN-9-OL	13835308	183741
(S)-(-)-PERILLYL ALCOHOL	536594	218391
TERPINEN-4-OL	562743	218383
ALPHA-TERPINEOL	98555	218375
(+/-)-TRANS-P-MENTH-6-ENE-2,3-DIOL	32226543	247774
CYCLOHEPTANEMETHANOL	4448753	138657
TETRAHYDROFURFYL ALCOHOL	97994	185396
(S)-(+)-PYRROLIDINEMETHANOL	23356969	186511
1-METHYL-2-PYRROLIDINEETHANOL	67004642	139513
1-ETHYL-4-HYDROXYPYPERIDINE	3518830	224634
3-HYDROXYPYPERIDINE HYDROCHLORIDE	64051792	174416
(+/-)-2-PIPERIDINEMETHANOL	3433372	155225
3-PIPERIDINEMETHANOL	4606659	155233
1-METHYL-2-PIPERIDINEMETHANOL	20845345	155241
1-METHYL-3-PIPERIDINEMETHANOL	7583531	146145
2-PIPERIDINEETHANOL	1484840	131520
4-HYDROXYPYPERIDINE	5382161	128775
4-METHYL-1-PIPERAZINEPROPANOL	5317339	238716
EXO-NORBORNEOL	497370	179590

TABLE 26-continued

Exemplary Compounds of Formula R ₅ -OH (CAS No./Aldrich No.)		
5 ENDO-NORBORNEOL	497369	186457
5-NORBORNENE-2-METHANOL	95125	248533
(+/-)-3-METHYL-2-NORBORNANEMETHANOL	6968758	130575
((1S)-ENDO)-(-)-BORNEOL	464459	139114
(1R)-ENDO-(+)-FENCHYL ALCOHOL	2217029	196444
9-ETHYLBICYCLO[3.3.1]NONAN-9-OL	21951333	193895
10 (+/-)-ISOPINOCAMPHEOL	51152115	183229
(S)-CIS-VERBENOL	18881044	247065
(1R,2R,3R,5S)-(-)-ISOPINOCAMPHEOL	25465650	221902
(1R)-(-)-MYRHENOL	515004	188417
1-ADAMANTANOL	768956	130346
3,5-DIMETHYL-1-ADAMANTANOL	707379	231290
15 2-ADAMANTANOL	700572	153826
1-ADAMANTANEETHANOL	770718	184209
1-ADAMANTANEETHANOL	6240115	188115
3-FURANMETHANOL	4412913	196398
FURFURYL ALCOHOL	98000	185930
2-(3-THIENYL)ETHANOL	13781674	228796
4-METHYL-5-IMIDAZOLEMETHANOL	38585625	227420
20 HYDROCHLORIDE	443481	226742
METRONIDAZOLE	32673419	219908
4-(HYDROXYMETHYL)IMIDAZOLE	3279763	128740
HYDROCHLORIDE	586958	151629
4-METHYL-5-THIAZOLEETHANOL	137008	190675
2-(2-HYDROXYETHYL)PYRIDINE	103742	128643
25 2-HYDROXY-6-METHYL PYRIDINE	3279763	128740
4-PYRIDYL CARBINOL	586958	151629
3-PYRIDYL CARBINOL N-OXIDE	6968725	184446
1-BENZYL-4-HYDROXYPYPERIDINE	4727724	152986
1-(4-CHLOROPHENYL)-1-CYCLOPENTANEETHANOL	80866791	188697
30 (4S,5S)-(-)-2-METHYL-5-PHENYL-2-OXAZOLINE-4-METHANOL	53732415	187666
6-(4-CHLOROPHENYL)-4,5-DIHYDRO-2-(2-HYDROXYBUTYL)-3(2H)-PYRIDAZINONE	38958826	243728
N-(2-HYDROXYETHYL)PHthalimide	3891074	138339
2-NAPHTHALENEETHANOL	1485070	188107
35 1-NAPHTHALENEETHANOL	773999	183458
2-ISOPROPYLPHENOL	88697	129526
4-CHLORO-ALPHA,ALPHA-DIMETHYLPHENETHYL ALCOHOL	5468973	130559
4-FLUORO-ALPHA-METHYL BENZYL ALCOHOL	403418	132705
3-PHENYL-1-PROPANOL	122974	140856
3-(4-METHOXYPHENYL)-1-PROPANOL	5406188	142328
4-FLUOROPHENETHYL ALCOHOL	7589277	154172
4-METHOXYPHENETHYL ALCOHOL	702238	154180
TRANS-2-METHYL-3-PHENYL-2-PROPEN-1-OL	1504558	155888
2-ANILINOETHANOL	122985	156876
3-FLUOROBENZYL ALCOHOL	456473	162507
2-FLUOROBENZYL ALCOHOL	446515	162515
2-METHYL-1-PHENYL-2-PROPANOL	100867	170277
ALPHA-(CHLOROMETHYL)-2,4-DICHLOROBENZYL ALCOHOL	13692143	178403
2-PHENYL-1-PROPANOL	1123859	179817
4-CHLOROPHENETHYL ALCOHOL	1875883	183423
50 4-BROMOPHENETHYL ALCOHOL	4654391	183431
4-NITROPHENETHYL ALCOHOL	100276	183466
2-NITROPHENETHYL ALCOHOL	15121843	183474
BETA-ETHYLPHENETHYL ALCOHOL	2035941	183482
4-PHENYL-1-BUTANOL	3360416	184756
2-METHOXYPHENETHYL ALCOHOL	7417187	187925
55 3-METHOXYPHENETHYL ALCOHOL	5020417	187933
3-PHENYL-1-BUTANOL	2722363	187976
2-METHYLPHENETHYL ALCOHOL	19819988	188123
3-METHYLPHENETHYL ALCOHOL	1875894	188131
4-METHYLPHENETHYL ALCOHOL	699025	188158
5-PHENYL-1-PENTANOL	10521912	188220
4-(4-METHOXYPHENYL)-1-BUTANOL	22135508	188239
4-(4-NITROPHENYL)-1-BUTANOL	79524202	188751
3,3-DIPHENYL-1-PROPANOL	20017678	188972
1-PHENYL-2-PROPANOL	14898874	189235
(+/-)-ALPHA-ETHYLPHENETHYL ALCOHOL	701702	190136
1,1-DIPHENYL-2-PROPANOL	29338496	190756
3-CHLOROPHENETHYL ALCOHOL	5182445	193518
4-METHYL-2-CHLOROPHENETHYL ALCOHOL	19819955	193844
(+/-)-1-PHENYL-2-PENTANOL	705737	195286

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TABLE 26-continued

Exemplary Compounds of Formula R ₃ -OH (CAS No./Aldrich No.)			
2,2-DIPHENYLETHANOL	1883325	196568	
4-ETHOXY-3-METHOXYPHENETHYL	77891293	197599	
ALCOHOL			5
3,4-DIMETHOXYPHENETHYL ALCOHOL	7417212	197653	
3-(3,4-DIMETHOXYPHENYL)-1-PROPANOL	3929473	197688	

TABLE 26-continued

Exemplary Compounds of Formula R ₃ -OH (CAS No./Aldrich No.)			
2-(4-BROMOPHENOXY)ETHANOL	34743889	198765	
2-FLUOROPHENETHYL ALCOHOL	50919067	228788	
3-(TRIFLUOROMETHYL)PHENETHYL ALCOHOL	455016	230359	
2-(PHENYLTHIO)ETHANOL	699127	232777	10
1-(2-METHOXYPHENYL)-2-PROPANOL	15541261	233773	

TABLE 27

Exemplary Method Embodiments of Processes A-R

A; B; C; D; AB; AC; AD; BC; BD; CD; ABC; ACD; ABD; BCD; ABCD;
 E; F; G; H; EF; EG; EH; FG; FH; GH; EFG; EGH; EFGH; ED; FD; GD;
 HD; EFD; EGD; EHD; FGD; FHD; GHG; EFGD; EGHG; EFHD; FGHD; EFGHD;
 I; J; K; L; M; II; IK; IL; IM; JK; JL; JM; KL; KM; LM; UK; IL; DM; IKL; IKM; ILM;
 JKL; JLM; KLM; UKL; IKLM; ULM; JKLM; UKML;
 N; O; P; NO; NP; OP; NOP;
 Q; R; QR;
 AI; AJ; AK; AL; AM; AJI; AIL; AIM; AJK; AJL; AJM; AKL; AKM; ALM;
 AJK; AJL; AJM; AIKL; AIKM; AILM; AJKL; AJLM; AKLM; AJKL; AIKLM;
 AILM; AJKLM; AJKML; A
 BI; BJ; BK; BL; BM; BII; BIK; BIL; BIM; BJK; BJL; BJM; BKL; BKM; BLM; BJK;
 BIJL; BIM; BIKL; B4KM; BILM; BJKL; BJLM; BKLM; BJKL; BIKLM; BULM;
 BJKLM; BJKML; B
 CI; CJ; CK; CL; CM; CIJ; CIL; CIM; CJK; CJL; CJM; CKL; CKM; CLM; CIJK;
 CJL; CJM; CJKL; CIKM; CILM; CJKL; CJLM; CKLM; CJKL; CILM; CJLM;
 CJKLM; CJKML; C
 DI; DJ; DK; DL; DM; DJI; DIK; DIL; DIM; DJK; DJL; DJM; DKL; DKM; DLM;
 DJK; DJL; DJM; DIKL; DIKM; DILM; DJKL; DJLM; DKLM; DJKL; DIKL; DIKLM;
 DJLM; DJKL; DJKML; D
 ABI; ABJ; ABK; ABL; ABM; ABII; ABIK; ABIL; ABIM; ABJK; ABJL; ABJM;
 ABKL; ABKM; ABLM; ABIJK; ABIL; ABIM; ABIKL; ABIKM; ABILM;
 ABJKL; ABJLM; ABKLM; ABUKL; ABIKL; ABJLM; ABKLM; ABUKML; AB
 ACI; ACJ; ACK; ACM; ACI; ACIK; ACIL; ACIM; ACJK; ACJL; ACJM;
 ACKL; ACKM; ACM; ACUK; ACIL; ACJM; ACIKL; ACIKM; ACILM;
 ACJKL; ACJLM; ACKLM; ACIJKL; ACIKLM; ACIJLM; ACJKLM; ACIKLM; AC
 ADI; ADJ; ADK; ADL; ADM; ADI; ADIK; ADIL; ADM; ADJK; ADJL; ADJM;
 ADKL; ADKM; ADLM; ADIJK; ADIL; ADIM; ADIKL; ADIKM; ADILM;
 ADJKL; ADJLM; ADKLM; ADIJKL; ADIKLM; ADIULM; ADJKLM; ADIJKM;
 AD
 BCI; BCJ; BCK; BCL; BCM; BCII; BCIK; BCIL; BCIM; BCJK; BCJL; BCJM; BCKL;
 BCKM; BCLM; BCIIK; BCIL; BCIM; BCIKM; BCILM; BCJKL; BCJLM;
 BCCKL; BCJUKL; BCJIKL; BCJILM; BCJJKL; BCJJKML; BC
 BDI; BDJ; BDK; BDL; BDM; BDI; BDIK; BDIL; BDIM; BDJK; BDJL; BDJM;
 BDKL; BDKM; BDLM; BDIK; BDUL; BDIIM; BDIKL; BDILM; BDJKL;
 BDJLM; BDJKL; BDJKLM; BDJLM; BDJKML; BD
 CDI; CDJ; CDK; CDL; CDM; CDI; CDIK; CDIL; CDIM; CDJK; CDJL; CDJM;
 CDKL; CDM; CDLM; CDIJK; CDJL; CDIM; CDIKL; CDIKM; CDILM; CDJKL;
 CDJLM; CDKLM; CDIJKL; CDIJKM; CDJLM; CDJKLM; CDIJKML; CD
 ABCI; ABCJ; ABCK; ABCL; ABCM; ABCI; ABCIK; ABCIL; ABCIM; ABCJK;
 ABCIL; ABCJM; ABCKL; ABCKM; ABCLM; ABCIKL; ABCJL; ABCJM;
 ABCIKL; ABCIKM; ABCILM; ABCJKL; ABCJLM; ABCKLM; ABCJKL;
 ABCIJKL; ABCIJKM; ABCJKLM; ABCIJKML; ABC
 ACDI; ACDJ; ACDK; ACDL; ACDM; ACDU; ACDK; ACDIL; ACDIM; ACDJK;
 ACDIL; ACDJM; ACDKL; ACDKM; ACDLM; ACDJK; ACDIL; ACDJM;
 ACDIKL; ACDIKM; ACDILM; ACDJKL; ACDJLM; ACDKLM; ACDJKL;
 ACDIJKM; ACDIJKL; ACDIJKM; ACDIJKL; ACD
 ABDI; ABDJ; ABDK; ABDL; ABDM; ABDU; ABDK; ABDIL; ABDIM; ABDJK;
 ABDJL; ABDJM; ABDKL; ABDKM; ABDLM; ABDJK; ABDIL; ABDIM;
 ABDIKL; ABDIKM; ABDILM; ABDJKL; ABDJLM; ABDKLM; ABDJKL;
 ABDIJKL; ABDIULM; ABDJKLM; ABDIJKML; ABD
 BCDI; BCDJ; BCDK; BCDL; BCDM; BCDI; BCDIK; BCDIL; BCDIM; BCDJK;
 BCDJL; BCDJM; BCDKL; BCDKM; BCDLM; BCDJK; BCDJL; BCDIM; BCDIKL;
 BCDIKM; BCDILM; BCDJKL; BCDJLM; BCDKLM; BCDJKL; BCDIKLM;
 BCDJLM; BCDJKLM; BCDIJKML; BCD
 ABCDI; ABCDJ; ABCDK; ABCDL; ABCDM; ABCDIJ; ABCDIK; ABCDIL;
 ABCDIM; ABCDJK; ABCDJL; ABCDJM; ABCDKL; ABCDKM; ABCDLM;
 ABCDIJK; ABCDIIL; ABCDIJM; ABCDIKL; ABCDIKM; ABCDIILM; ABCDIJKL;
 ABCDIJLM; ABCDKLM; ABCDIJKL; ABCDIKLM; ABCDIJLM; ABCDIJKLM;
 ABCDIJKML; ABCD

TABLE 27-continued

Exemplary Method Embodiments of Processes A-R

TABLE 27-continued

Exemplary Method Embodiments of Processes A–R

FGDI; FGDJ; FGDK; FGDL; FGDM; FGDI; FGDIK; FGDL; FGDIM; FGDIK;
FGDIL; FGDJM; FGDKL; FGDKM; FGDLM; FGDIJK; FGPIJL; FGDIJM; FGDIKL;
FGDIKM; FGDLM; FGDIJKL; FGDLJM; FGDKLM; FGDIJKL; FGDIKLM;
FGDIJLM; FGDKJLM; FGDIJKML; FGD
FHD; FHDJ; FHDK; FHDL; FHDML; FHDIJ; FHDIK; FHDL; FHDIM; FHDIK;
FHDL; FHDJM; FHDKL; FHDKM; FHDL; FHDIK; FHDL; FHDIJ; FHDIJM;
FHDL; FHDIK; FHDIKM; FHDL; FHDKL; FHDLJM; FHDKLM; FHDIJKL;
FHDIKLM; FHDLJM; FHDKLM; FHDIJKML; FHD
GHD; GHDI; GHDK; GHDL; GHDM; GHDIJ; GHDIK; GHDL; GHDM;
GHDIK; GHDL; GHDM; GHDKL; GHDKM; GHDL; GHDIK; GHDL;
GHDM; GHDIK; GHDIKM; GHDL; GHDKL; GHDLJM; GHDKLM;
GHDL; GHDIKLM; GHDLJM; GHDKLM; GHDIJKML; GH
EFGDI; EFGDJ; EFGDK; EFGDL; EFGDM; EFGDIJ; EFGDIK; EFGDL; EPGDIM;
EFGDJ; EFGDJL; EPGDM; EFGDKL; EFGDKM; EFGDL; EFGDIJK; EFGDL;
EFGDLM; EFGDIKL; EFGDIKM; EFGDLJM; EFGDIJKL; EFGDLJM; EFGDKLM;
EFGDIJKL; EFGDLJM; EFGDKLM; EFGDIJKL; EFGDIKLM; EFGD
EGHDI; EGHDI; EGHDK; EGHDL; EGHDM; EGHDIJ; EGHDIK; EGHDL;
EGHDIM; EGHDIK; EGHDL; EGHDM; EGHDIK; EGHDIKM; EGHDL; EGHDM;
EGHDIJK; EGHDL; EGHDM; EGHDIK; EGHDIJM; EGHDL; EGHDIJKL;
EGHDILM; EGHDKLM; EGHDIJKL; EGHDIKLM; EGHDIJLM; EGHDIJKLM;
EGHDIJKML; EGH
EFHDI; EFHD; EFHDK; EFHDL; EFHDM; EFHDIJ; EFHDIK; EFHDIL; EFHDIM;
EFHDJK; EFHDIL; EFHDJM; EFHDKL; EFHDKM; EFHDLM; EFHDJK;
EFHDIL; EFHDJM; EFHDIKL; EFHDIKM; EFHDILM; EFHDJKL; EFHDJLM;
EFHDKLM; EFHDJKL; EFHDIKLM; EFHDJLM; EFHDJKLM; EFHDUKML;
EFHD
FGHDI; FGHDJ; FGHDK; FGHDL; FGHDM; FGHDU; FGHDIK; FGHDIL;
FGHDIM; FGHDJK; FGHDIL; FGHDJM; FGHDKL; FGHDKM; FGHDLM;
FGHDJK; FGHDIL; FGHDJM; FGHDIK; FGHDIKM; FGHDILM; FGHDJKL;
FGHDJLM; FGHDKLM; FGHDJKL; FGHDIKLM; FGHDJLM; FGHDJKLM;
FGHDJKML; FGHD
EFGHDI; EFGHDJ; EFGHDK; EFGHDL; EFGHDM; EFGHDU; EFGHDIK;
EFGHDIL; EFGHDIM; EFGHDJK; EFGHDIL; EFGHDJM; EFGHDKL;
EFGHDKM; EFGHDLM; EFGHDJK; EFGHDIL; EFGHDJM; EFGHDJKL;
EFGHDIKM; EFGHDILM; EFGHDJKL; EFGHDJLM; EFGHDKLM; EFGHDJKL;
EFGHDJKLM; EFGHDILM; EFGHDJKL; EFGHDUKML; EFGHD

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Modification of the exemplary starting materials to form different E₁ groups has been described in detail and will not be elaborated here. See Fleet, G. W. J. et al.; "J. Chem. Soc. Perkin Trans. I", 905-908 (1984); Fleet, G. W. J. et al.; "J. Chem. Soc., Chem. Commun.", 849-850 (1983); Yee, Ying K. et al.; "J. Med. Chem.", 33:2437-2451 (1990); Olson, R. E. et al.; "Bioorganic & Medicinal Chemistry Letters", 4(18):2229-2234 (1994); Santella, J. B. III et al.; "Bioorganic & Medicinal Chemistry Letters", 4(18):2235-2240 (1994); Judd, D. B. et al.; "J. Med. Chem.", 37:3108-3120 (1994) and Lombaert, S. De et al.; "Bioorganic & Medicinal Chemistry Letters", 5(2):151-154 (1994), each of which is incorporated herein by reference in its entirety.

The E_1 sulfur analogs of the carboxylic acid compounds of the invention are prepared by any of the standard techniques. By way of example and not limitation, the carboxylic acids are reduced to the alcohols by standard methods. The alcohols are converted to halides or sulfonic acid esters by standard methods and the resulting compounds are reacted with NaSH to produce the sulfide product. Such reactions are described in Patai, "The Chemistry of the Thiol Group" (John Wiley, New York, 1974), pt. 2, and in particular pages 721-735.

Modifications of each of the above schemes leads to various analogs of the specific exemplary materials produced above. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the above exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified

(hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, size exclusion or ion exchange chromatography, high, medium, or low pressure liquid chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents 50 include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective 55 chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, 60 presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

65 Each of the cited works herein are incorporated by reference in their entirety. Specifically cited sections or pages of the above cited works are incorporated by reference

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with specificity. The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following claims. It is apparent that certain modifications of the methods and compositions of the following claims can be made within the scope and spirit of the invention.

EXAMPLES**General**

The following Examples refer to the Schemes.

Example 1

Epoxy alcohol 1: Prepared from shikimic acid by the procedure of McGowan and Berchtold, "J. Org. Chem.", 46:2381 (1981).

Example 2

Epoxy allyl ether 2: To a solution of epoxy alcohol 1 (2.37 g, 14.08 mmol) in dry benzene (50 mL) was added thallium (I)ethoxide (1.01 mL) in one portion. After 2 hr the reaction was concentrated in vacuo and the residue dissolved in acetonitrile. Allyl iodide (3.0 mL) was added and the mixture was stirred in the dark for 16 h. The solids were filtered thru a celite pad and washed with chloroform. Concentration in vacuo followed by flash chromatography (40% EtOAc in hexane) gave 1.24 g (42%) of 2 as a pale viscous oil.

¹H NMR (300 MHz, CDCl₃): δ 6.75 (1H, m); 6.10–5.90 (1H, m, —CH=, allyl); 5.40–5.15 (2H, m, =CH₂, allyl); 4.47–4.43 (1H, m); 4.30–4.15 (2H, m, —CH₂—, allyl); 3.73 (3H, s); 3.55–3.50 (1H, m); 3.45–3.40 (1H, m); 3.15–3.00 (1H, dm, J=19.5 Hz); 2.50–2.35 (1H, dm, J=2.7, 19.5 Hz).

Example 3

Azido alcohol 3: Epoxide 2 (1.17 g, 5.57 mmol), sodium azide (1.82 g) and ammonium chloride (658 mg) were refluxed in MeOH/H₂O (8:1) (35 mL) for 18 h. The reaction was then concentrated in vacuo and the residue partitioned between ethyl ether and water. The organic layer was washed with brine and dried. Concentration in vacuo gave 3 as a pale oil 1.3 g (92%) which was used without further purification.

¹H NMR (300 MHz, CDCl₃): δ 6.95–6.85 (1H, m); 6.00–5.85 (1H, m, —CH=, allyl); 5.35–5.25 (2H, m, =CH₂, allyl); 4.25–4.10 (2H, m, —CH₂—, allyl); 4.12 (1H, bt, J=4.2 Hz); 3.95–3.75 (2H, m); 3.77 (3H, s); 2.85 (1H, dd, J=5.3, 18.3 Hz); 2.71 (1H, bs); 2.26 (1H, dd, J=7.2, 18.3 Hz).

Example 4

Aziridine 4: To a solution of alcohol 3 (637 mg, 2.52 mmol) in CH₂Cl₂ (20 mL) cooled to 0° C. was added DMAP (few crystals) and triethyl amine (442 μ L). MsCl (287 μ L) was then added and the reaction stirred for 2 h at 0° C. Volatiles were removed and the residue partitioned between ethyl ether and water. The organic layer was washed with saturated bicarbonate, brine and then dried. Concentration in vacuo gave 881 mg of crude mesylate.

¹H NMR (300 MHz, CDCl₃): δ 6.87–6.84 (1H, s); 6.00–5.85 (1H, m, —CH=, allyl); 5.40–5.25 (2H, m, =CH₂, allyl); 4.72 (1H, dd, J=3.9, 8.5 Hz); 4.32 (1H, bt, J=3.9 Hz); 4.30–4.15 (2H, m, —CH₂—, allyl); 3.77 (3H, s); 3.14 (3H, s); 2.95 (1H, dd, J=5.7, 18.6 Hz); 2.38 (1H, dd, J=6.7, 18.6 Hz).

The crude mesylate was dissolved in dry THF (20 mL) and treated with Ph₃P (727 mg). After stirring for 3 h at room temperature, water (15 mL) and solid NaHCO₃ (1.35 g) was

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added and the mixture stirred overnight at room temperature. The reaction was then concentrated in vacuo and the residue partitioned between EtOAc, saturated bicarbonate and brine. The organic layer was separated and dried over MgSO₄. Concentration in vacuo and flash chromatography of the residue gave the aziridine 4 170 mg (33%) as a pale yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 6.82–6.80 (1H, m); 6.04–5.85 (1H, m, —CH=, allyl); 5.35–5.20 (2H, m, =CH₂, allyl); 4.39 (1H, bd, J=2.4 Hz); 4.20–4.05 (2H, m, —CH₂—, allyl); 3.73 (3H, s); 2.90–2.80 (1H, bd, J=18.9 Hz); 2.65–2.40 (2H, m).

Example 5

N-acetyl aziridine 5: Aziridine 4 (170 mg, 0.814 mmol) was dissolved in CH₂Cl₂ (2 mL) and pyridine (4 mL) and cooled to 0° C. Acetyl chloride (87 μ L) was then added and the reaction stirred at 0° C. for 1 h. Volatiles were removed in vacuo and the residue partitioned between ethyl ether, saturated bicarbonate and brine. The organic layer was separated and dried over MgSO₄. Concentration gave crude 5 196 mg (96%) which was used without further purification.

¹H NMR (300 MHz, CDCl₃): δ 6.88–6.86 (1H, m); 6.00–5.85 (1H, m, —CH=, allyl); 5.40–5.20 (2H, m, =CH₂, allyl); 4.45–4.40 (1H, m); 4.16 (2H, d, J=6.0 Hz, —CH₂—, allyl); 3.76 (3H, s); 3.00–2.95 (2H, m); 2.65 (1H, bd, J=18.5 Hz); 2.14 (3H, s).

Example 6

Azido allyl ether 6: Aziridine 5 (219 mg, 0.873 mmol), sodium azide (426 mg) and ammonium chloride (444 mg) in dry DMF (7 mL) was heated at 65° C. under argon overnight. The reaction was poured into saturated bicarbonate/brine and extracted with ethyl ether several times. The combined ether layers were washed with brine and dried. Concentration followed by flash chromatography (EtOAc only) gave the azido amine 77 mg (35%) which was dissolved in CH₂Cl₂ (1 mL) and pyridine (1 mL) and cooled to 0° C. Acetyl chloride (38 μ L) was added and after 45 min solid NaHCO₃ was added and the volatiles removed under vacuum. The residue was partitioned between EtOAc and brine. The organic layer was dried over MgSO₄ and concentrated in vacuo. Flash chromatography (EtOAc only) gave 6 90 mg (99%).

¹H NMR (500 MHz, CDCl₃): δ 6.86 (1H, bt, J=2.2 Hz); 5.95–5.82 (1H, m, CH=, allyl); 5.68 (1H, bd, J=7.3 Hz); 5.35–5.20 (2H, m, =CH₂, allyl); 4.58–4.52 (1H, m, 4.22–4.10 (2H, m); 4.04 (1H, dd, J=5.9, 12.5 Hz); 3.77 (3H, s); 3.54–3.52 (1H, m); 2.89 (1H, dd, J=5.9, 17.6 Hz); 2.32–2.22 (1H, m); 2.06 (3H, s).

Example 7

Azido diol 7: To a solution of olefin 6 (90 mg, 0.306 mmol) in acetone (3 mL) and water (258 μ L) was added N-methyl morpholine-N-oxide (39 mg) and OsO₄ (73 μ L of a 2.5% w/w in t-butanol). The reaction was then stirred at room temperature for 3 days. Solid sodium hydrosulfite was added and after stirring for 20 min the reaction was filtered thru a celite pad and washed with copious amounts of acetone. Concentration in vacuo followed by flash chromatography (10% MeOH in CH₂Cl₂) gave the diol 7 50 mg (50%).

¹H NMR (300 MHz, CD₃CN): δ 6.80–6.70 (1H, m); 4.20–4.15 (1H, bm); 3.95–3.80 (1H, m); 3.80–3.25 (6H, m);

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3.70 (3H, s); 3.10 (1H, bs); 2.85 (1H, bs); 2.85–2.75 (1H, m); 2.30–2.15 (1H, m); 2.16 (1H, bs); 1.92 (3H, s).

Example 8

Amino acid diol 8: A solution of the diol 7 (23 mg, 0.07 mmol) in THF (1 mL) was treated with aq. KOH (223 μ L, of 0.40M solution) at room temperature. After stirring for 1.5 h the reaction was acidified to pH=4 with Amberlite IR-120 (plus) ion exchange resin. The resin was filtered and washed with MeOH. Concentration in vacuo gave the crude carboxylic acid which was dissolved in ethanol (1.5 mL). To this solution was added Lindlar's catalyst (20 mg) and the reaction stirred over a hydrogen atmosphere (1 atm via a balloon) for 20 h. The reaction mixture was filtered thru a celite pad and washed with hot ethanol and water. The ethanol was removed under vacuum and the resulting aqueous layer lyophilized to give a mixture of the desired amino acid 8 and the starting azide 7 as a white powder. Compound 8: 1 H NMR (500 MHz, D_2 O): δ 6.5 (1H, s); 4.24–4.30 (2H, m); 4.25–4.18 (1H, m); 3.90–3.55 (5H, complex m); 2.96–2.90 (1H, m); 2.58–2.50 (1H, complex m); 2.12 (3H, s).

Example 9

Compound 62: A suspension of Quinic acid (60 g), cyclohexanone (160 mL) and toluenesulfonic acid (600 mg) in benzene (450 mL) was refluxed with Dean-Stark for 14 hrs. The reaction mixture was cooled to room temperature and poured into saturated $NaHCO_3$ solution (150 mL). The aqueous layer was extracted with CH_2Cl_2 (3 \times). The combined organic layers were washed with water (2 \times), brine (1 \times), and dried over Na_2SO_4 . Concentration gave a whited solid, which was recrystallized from ether (75 g, 95%): 1 H NMR ($CDCl_3$) δ 4.73 (dd, J =6.1, 2.5 Hz, 1H), 4.47 (ddd, J =7.0, 7.0, 3.0 Hz, 1H), 4.30 (ddd, J =5.4, 2.6, 1.4 Hz, 1H), 2.96 (s, 1H), 2.66 (d, J =11.7 Hz, 1H), 2.40–2.15 (m, 3H), 1.72–1.40 (m, 10H).

Example 10

Compound 63: To a solution of lactone 62 (12.7 g, 50 mmol) in methanol (300 mL) was added sodium methoxide (2.7 g, 50 mmol) in one portion. The mixture was stirred at room temperature for 3 hrs, and quenched with acetic acid (3 mL) and stirred for 10 min. The mixture was poured into saturated NH_4Cl solution (300 mL), and extracted with CH_2Cl_2 (3 \times). The combined organic phase was washed with brine (1 \times), and dried over $MgSO_4$. Purification by flash column chromatography (Hexane/EtOAc=1/1 to 1/2) gave diol (11.5 g, 80%) and starting material (1.2 g, 10%): 1 H NMR ($CDCl_3$) δ 4.47 (ddd, J =7.4, 5.8, 3.5 Hz, 1H), 4.11 (m, 1H), 3.98 (m, 1H), 3.81 (s, 3H), 3.45 (s, 1H), 2.47 (d, J =3.3 Hz, 1H), 2.27 (m, 2H), 2.10 (dd, J =11.8, 4.3 Hz, 1H), 1.92–1.26 (m, 10H).

Example 11

Compound 64: To a mixture of diol 63 (1.100 g, 3.9 mmol), molecule sieves (3 A, 2.2 g) and pyridine (1.1 g) in CH_2Cl_2 (15 mL) was added PCC (3.3 g, 15.6 mmol) in one portion. The mixture was stirred at room temperature for 26 hrs, and diluted with ether (30 mL). The suspension was filtered through a pad of celite, and washed with ether (2 \times 20 mL). The combined ether was washed with brine (2 \times), and dried over $MgSO_4$. Concentration and purification was by flash column chromatography (Hexane/EtOAc=3/1) gave the ketone (0.690 g, 67%): 1 H NMR ($CDCl_3$) δ 6.84 (d, J =2.8

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Hz, 1H), 4.69 (ddd, J =6.4, 4.9, 1.6 Hz, 1H), 4.30 (d, J =5.0 Hz, 1H), 3.86 (s, 3H), 3.45 (d, J =22.3 Hz, 1H), 2.86 (m, 1H), 1.69–1.34 (m, 10H).

Example 12

Compound 28: To a solution of ketone 64 (0.630 g, 2.4 mmol) in MeOH (12 mL) at 0° C. was added $NaBH_4$ in 30 min. The mixture was stirred for additional 1.5 hrs at 0° C., and quenched with 15 mL of saturated NH_4Cl solution. The solution was extracted with CH_2Cl_2 (3 \times), and the combined organic extract was dried over $MgSO_4$. Purification by flash column chromatography (Hexane/EtOAc=2/1) gave the alcohol (0.614 g, 97%): 1 H NMR ($CDCl_3$) δ 6.94 (d, J =0.5 Hz, 1H), 4.64 (ddd, J =9.8, 6.7, 3.2 Hz, 1H), 4.55 (dd, J =7.1, 4.2 Hz, 1H), 4.06 (m, 1H), 3.77 (s, 3H), 3.04 (dd, J =16.5, 2.1 Hz, 1H), 2.73 (d, J =10.2 Hz, 1H), 1.94 (m, 1H), 1.65–1.29 (m, 10H).

Example 13

Compound 66: Alcohol 28 (2.93 g, 10.9 mmol) and toluenesulfonic acid (1.5 g) were dissolved in acetone (75 mL), and the mixture was stirred at room temperature for 15 hrs. The reaction was quenched with water (30 mL), and basified with concentrated NH_3 — H_2O until PH=9. Acetone was removed under reduced pressure, and the water phase was extracted with CH_2Cl_2 (3 \times). The combined organic extracts were washed with brine (1 \times), and dried over Na_2SO_4 . Concentration gave the desired product: 1 H NMR ($CDCl_3$) δ 7.01 (m, 1H), 4.73 (m, 1H), 4.42 (m, 1H), 3.97 (m, 1H), 3.76 (s, 3H), 2.71–2.27 (m, 2H), 2.02 (s, 3H), 1.98 (s, 3H).

Example 14

Compound 67: To a solution of alcohol 66 (10.9 mmol) in CH_2Cl_2 (60 mL) at 0° C. was added pyridine (4.4 mL, 54.5 mmol), followed by addition of trimethylacetyl chloride (2.7 mL, 21.8 mmol). The mixture was warmed to room temperature and stirred for 14 hrs. The mixture was diluted with CH_2Cl_2 , and washed with water (2 \times), brine (1 \times), and dried over $MgSO_4$. Purification by flash column chromatography (Hexane/EtOAc=9/1) gave the diester (2.320 g, 68%): 1 H NMR ($CDCl_3$) δ 6.72 (m, 1H), 5.04 (m, 1H), 4.76 (m, 1H), 4.40 (m, 1H), 3.77 (s, 3H), 2.72–2.49 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 1.23 (s, 9H).

Example 15

Compound 68: Diester 67 (2.32 g, 2.3 mmol) was dissolved in acetone/ H_2O (1/1, 100 mL) and heated at 55° C. for 16 hrs. Solvents were removed, water (2 \times 50 mL) was added and evaporated. Concentration with toluene (2 \times 50 mL) gave diol, which was used without further purification: 1 H NMR ($CDCl_3$) δ 6.83 (m, 1H), 5.06 (m, 1H), 4.42 (m, 1H), 4.09 (m, 1H), 3.77 (s, 3H), 2.68–2.41 (m, 2H), 1.22 (s, 9H).

Example 16

Compound 69: To a solution of diol 68 (0.410 g, 1.5 mmol) in THF (8 mL) at 0° C. was added triethylamine (0.83 mL, 6.0 mmol), followed by slow addition of thionyl chloride (0.33 mL, 4.5 mmol). The mixture was warmed to room temperature and stirred for 3 hrs. The mixture was diluted with $CHCl_3$, and washed with water (3 \times), brine (1 \times), and dried over $MgSO_4$. Purification by flash column chromatography (Hexanes/EtOAc=5/1) gave a exo/endo mixture (0.430 g, 90%): 1 H NMR ($CDCl_3$) δ 6.89–6.85 (m, 1H),

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5.48–4.84 (m, 3H), 3.80, 3.78 (s, 3H), 2.90–2.60 (m, 2H), 1.25, 1.19 (s, 9H).

Example 17

Compound 70: The mixture of sulfone 69 (0.400 g, 1.3 mmol) and sodium azide (0.410 g, 6.29 mmol) in DMF (10 mL) was stirred for 20 hrs. The reaction mixture was then diluted with ethyl acetate, washed with saturated NH_4Cl solution, water, brine, and dried over MgSO_4 . Concentration gave the azide (0.338 g, 90%): $^1\text{H NMR}$ (CDCl_3) δ 6.78 (m, 1H), 5.32 (m, 1H), 4.20 (m, 1H), 3.89 (m, 1H), 3.78 (s, 3H), 3.00–2.60 (m, 2H), 1.21 (s, 9H).

Example 18

Compound 71: To a solution of alcohol 70 (0.338 g, 1.1 mmol) in CH_2Cl_2 (11 mL) at 0° C. was added triethylamine (0.4 mL, 2.9 mmol), followed by slow addition of methylsulfonic chloride (0.18 mL, 2.3 mmol). The mixture was stirred at 0° C. for 30 min., and diluted with CH_2Cl_2 . The organic layer was washed with water (2 \times), brine, and dried over MgSO_4 . Purification by flash column chromatography (Hexane/EtOAc=3/1) gave the desired compound (0.380 g, 82%): $^1\text{H NMR}$ (CDCl_3) δ 6.82 (m, 1H), 5.44 (m, 1H), 4.76 (dd, J =7.3, 1.4 Hz, 1H), 4.48 (m, 1H), 3.80 (s, 3H), 3.11 (s, 3H), 2.82–2.61 (m, 2H), 1.21 (s, 9H).

Example 19

Compound 72: The mixture of azide 71 (0.380 g, 0.94 mmol) and triphenylphosphine (0.271 g, 1.04 mmol) in THF (19 mL) was stirred for 2 hrs. The reaction was quenched with water (1.9 mL) and triethylamine (0.39 mL, 2.82 mmol), and the mixture was stirred for 14 hrs. Solvents were removed under reduced pressure, and the mixture was used for next step. To a solution of above mixture in CH_2Cl_2 (20 mL) at 0° C. was added pyridine (0.68 mL, 8.4 mmol), followed by slow addition of acetyl chloride (0.30 mL, 4.2 mmol). The mixture was stirred at 0° C. for 5 min., and diluted with ethyl acetate. The mixture was washed with water (2 \times), brine (1 \times), dried over MgSO_4 . Purification by flash column chromatography (Hexanes/EtOAc=3/1) gave the aziridine (0.205 g, 83%): $^1\text{H NMR}$ (CDCl_3) δ 7.19 (m, 1H), 5.58 (m, 1H), 3.77 (s, 3H), 3.14 (m, 2H), 2.85 (dd, J =7.0, 1.6 Hz, 1H), 2.34 (m, 1H), 2.16 (s, 3H), 1.14 (s, 9H).

Example 20

Compound 73: The mixture of aziridine 72 (0.200 g, 0.68 mmol), sodium azide (0.221 g, 3.4 mmol), and ammonium chloride (0.146 g, 2.7 mmol) in DMF (10 mL) was stirred at room temperature for 14 hrs. Then the mixture was diluted with ethyl acetate, and washed with water (5 \times), brine (1 \times), and dried over MgSO_4 . Purification by flash column chromatography (hexanes/EtOAc=2/1) gave desired product and deacetyl amine (0.139 g). The mixture was dissolved in acetic anhydride (2 mL), and stirred for 2 hrs. Excess anhydride was removed under reduced pressure, and give the desired product (149 mg): $^1\text{H NMR}$ (CDCl_3) δ 6.76 (m, 1H), 5.53 (d, J =8.5 Hz, 1H), 5.05 (m, 1H), 4.31 (m, 1H), 4.08 (m, 1H), 3.79 (s, 3H), 2.91 (m, 1H), 2.51 (m, 1H), 1.99 (s, 3H), 1.20 (s, 9H).

Example 21

Compound 74: A solution of potassium hydroxide in $\text{MeOH}/\text{H}_2\text{O}$ (0.5M, 4.4 mL, 2.2 mmol) was added to ester 73 (149 mg, 0.44 mmol) and the mixture was stirred at room temperature for 3 hrs. The mixture was cooled to 0° C., and

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acidified with Amberlite (acidic) to $\text{pH}=3$ –4. The mixture was filtered, and washed with MeOH . Concentration gave the carboxylic acid as a white solid (73 mg, 69%): $^1\text{H NMR}$ (CD_3OD) δ 6.62 (m, 1H), 4.15 (m, 1H), 3.95–3.72 (m, 2H), 2.84 (dd, J =6.7, 1.4 Hz, 1H), 2.23 (m, 1H), 1.99 (s, 3H).

Example 22

Compound 75: The mixture of azide 74 (8 mg) and Pd—C (Lindlar) (15 mg) in ethanol (2 mL) was stirred under hydrogen for 16 hrs. The mixture was filtered through celite, washed with hot MeOH — H_2O (1/1). Concentration gave a solid. The solid was dissolved in water, and passed through a short C-8 column, and washed with water. Concentration gave a white solid (6 mg): $^1\text{H NMR}$ (D_2O) δ 6.28 (m, 1H), 4.06–3.85 (m, 3H), 2.83 (dd, J =17.7, 5.4 Hz, 1H), 2.35 (m, 1H), 2.06 (s, 3H).

Example 23

Compound 76: Carboxylic acid 74 (68 mg, 0.28 mmol) and diphenyldiazomethane (61 mg, 0.31 mmol) were dissolved in ethanol (12 mL), and stirred for 16 hrs. The reaction was quenched with acetic acid (0.5 mL), and the mixture was stirred for 10 min. Solvents were removed under reduced pressure. Purification by flash column chromatography (EtOAc) gave the ester (56 mg, 50%): $^1\text{H NMR}$ (CD_3OD) δ 7.36–7.23 (m, 10H), 6.88 (s, 1H), 6.76 (s, 1H), 4.21 (m, 1H), 3.93–3.79 (m, 2H), 2.89 (dd, J =17.7, 5.0 Hz, 1H), 2.34 (m, 1H), 2.00 (s, 3H).

Example 24

Compound 77: To a solution of alcohol 76 (20 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added pyridine (40 μL , 0.5 mmol), followed by addition of acetic anhydride (24 μL , 0.25 mmol). The mixture was stirred for 24 hrs, and solvents and reagents were removed under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc=1/2) gave the diester (20 mg, 91%): $^1\text{H NMR}$ (CDCl_3) δ 7.40–7.27 (m, 10H), 6.95 (s, 1H), 6.87 (m, 1H), 5.60 (m, 1H), 5.12 (ddd, J =16.4, 10.2, 5.9 Hz, 1H), 4.28 (dd, J =20.0, 9.4 Hz, 1H), 4.15 (m, 1H), 2.93 (dd, J =17.8, 5.2 Hz, 1H), 2.57 (m, 1H), 2.09 (s, 3H), 2.01 (s, 3H).

Example 25

Compound 78: The mixture of diester 77 (20 mg, 0.045 mmol), anisole (50 μL , 0.45 mmol), and TFA (1 mL) in CH_2Cl_2 (1 mL) was stirred for 20 min. Solvents and reagents were removed under reduced pressure. Purification by flash column chromatography (EtOAc to EtOAc/AcOH=100/1) gave the carboxylic acid (6 mg): $^1\text{H NMR}$ (CDCl_3) δ 6.85 (m, 1H), 5.54 (m, 1H), 5.12 (m, 1H), 4.31–4.03 (m, 2H), 2.89 (m, 1H), 2.60–2.41 (m, 1H), 2.11 (s, 3H), 2.03 (s, 3H).

Example 26

Compound 79: The mixture of azide 78 (6 mg, 0.02 mmol) and Pd—C (Lindlar) (15 mg) in $\text{EtOH}/\text{H}_2\text{O}$ (2.2 mL, 10/1) was stirred under hydrogen for 3 hrs. The mixture was filtered through a pad of celite, washed with hot $\text{MeOH}/\text{H}_2\text{O}$ (1/1). Evaporation gave a white solid. The solid was dissolved in water, and passed through a C-8 column. Evaporation of water gave a white powder (3 mg): $^1\text{H NMR}$ (D_2O) δ 6.32 (m, 1H), 5.06 (m, 1H), 4.06 (t, J =10.4 Hz, 1H), 3.84 (m, 1H), 2.83 (m, 1H), 2.42 (m, 1H), 2.06 (s, 3H), 2.00 (s, 3H).

Example 27

Compound 80: To a solution of alcohol 76 (35 mg, 0.086 mmol), Boc-glycine (30 mg, 0.172 mmol), and catalytic

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amount DMAP in CH_2Cl_2 (1 mL) was added DCC (35 mg, 0.172 mmol). The mixture was stirred for 30 min, and filtered and washed with CHCl_3 . The CHCl_3 solution was washed with water (2 \times). Concentration gave a white solid. Purification by flash column chromatography (Hexane/EtOAc=1/2) gave product (30 mg): ^1H NMR (CDCl_3) 87.39–7.26 (m, 10H), 6.95 (s, 1H), 6.86 (m, 1H), 5.77 (m, 1H), 5.27 (m, 1H), 4.99 (m, 1H), 4.18–4.01 (m, 2H), 3.94–3.84 (m, 2H), 2.96 (dd, J =7.8, 5.9 Hz, 1H), 2.57 (m, 1H), 2.02 (s, 3H), 1.45 (s, 9H).

Example 28

Compound 81: The mixture of diester 80 (30 mg, 0.05 mmol), anisole (150 μL), and TFA (1 mL) in CH_2Cl_2 (1 mL) was stirred for 3 hrs. Solvents and reagents were evaporated. The mixture was dissolved in water, and washed with CHCl_3 (3 \times). Water phase was evaporated to give a white solid (15 mg): ^1H NMR (CD_3OD) 86.73 (m, 1H), 5.25–5.15 (m, 1H), 4.35 (m, 1H), 4.17 (m, 1H), 3.82 (m, 2H), 2.93 (dd, J =17.7, 5.6 Hz, 1H), 2.42 (m, 1H), 1.97 (s, 3H).

Example 29

Compound 82: The mixture of azide 81 (15 mg, 0.05 mmol) and Pd—C (Lindlar) (30 mg) in $\text{EtOH}/\text{H}_2\text{O}$ (4 mL, 1/1) was stirred under hydrogen for 3 hrs. The mixture was filtered through a pad of celite, and washed with hot $\text{MeOH}/\text{H}_2\text{O}$ (1/1). Concentration gave a glass-like solid. The solid was dissolved in water, and passed through C-8 column. Evaporation of water gave the amino acid: ^1H NMR (D_2O) 86.68 (m, 1H), 5.28 (m, 1H), 4.29 (m, 1H), 4.08–3.79 (m, 3H), 2.85 (m, 1H), 2.41 (m, 1H), 2.04 (s, 3H).

Example 30

bis-Boc guanidinyl methyl ester 92: Treated according to the procedure of Kim and Qian, "Tetrahedron Lett.", 34:7677 (1993). To a solution of amine 91 (42 mg, 0.154 mmol), bis-Boc thiourea (43 mg, 0.155 mmol) and triethylamine (72 μL) in dry DMF (310 μL) cooled to 0° C. was added mercury chloride (46 mg, 0.170 mmol) in one portion. After 30 min the reaction was warmed to room temperature and stirred for an additional 2.5 h. The reaction mixture was then filtered through a celite pad, concentrated and purified by flash column chromatography (100% ethyl acetate) to give 70 mg (89%) of 92 as a colorless foam. ^1H NMR (CDCl_3 , 300 MHz): δ 11.37 (s, 1H); 8.60 (d, 1H, J =7.8 Hz); 6.83 (t, 1H, J =2.1 Hz); 6.63 (d, 1H, J =8.4 Hz); 4.76 (d, 1H, J =7.0 Hz); 4.71 (d, 1H, J =7.0 Hz); 4.45–4.10 (complex m, 2H); 3.76 (s, 3H); 3.39 (s, 3H); 2.84 (dd, 1H, J =5.4, 17.4 Hz); 2.45–2.30 (m, 1H); 1.92 (s, 3H); 1.49 (s, 18H).

Example 31

bis-Boc guanidinyl carboxylic acid 93: To a solution of ester 92 (70 mg, 0.136 mmol) in THF (3 mL) cooled to 0° C. was added aq. KOH (350 μL of a 0.476M solution). The reaction was then warmed to room temperature and stirred for 2 h. The reaction was then acidified to pH=4.5 with Amberlite IR-120 (plus) acidic resin. The resin was then filtered and washed with ethanol and H_2O . Concentration in vacuo gave 66 mg (97%) of carboxylic acid 93 as a white solid. ^1H NMR (CDCl_3 , 300 MHz): δ 11.40 (br s, 1H); 8.67 (d, 1H, J =7.8 Hz); 6.89 (s, 1H); 6.69 (br d, 1H, J =8.4 Hz); 4.77 (d, 1H, J =7.2 Hz); 4.70 (d, 1H, J =7.2 Hz); 4.40–4.15 (m, 2H); 3.39 (s, 3H); 2.84 (dd, 1H, J =4.8, 17.1 Hz); 2.45–2.30 (m, 1H); 1.95 (s, 3H); 1.49 (s, 9H); 1.48 (s, 9H).

Example 32

Guanidine carboxylic acid TFA salt 94: To a solution of bis-Boc guanidinyl carboxylic acid 93 (23 mg, 0.046 mmol)

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in CH_2Cl_2 (1 mL) cooled to 0° C. was added neat trifluoroacetic acid (500 μL). After 30 min the reaction was warmed to room temperature and stirred for an additional 1.25 h. Volatiles were removed under vacuum and the residue co-evaporated with several portions of H_2O to give a pale orange solid. The residue was purified by reverse phase C_{18} chromatography using H_2O as an eluent. Fractions containing the desired product were pooled and lyophilized to give 15 mg of 93 as a white powder. ^1H NMR (D_2O , 500 MHz): δ 86.82 (t, 1H, J =2.0 Hz); 4.51–4.47 (m, 1H); 3.93 (dd, 1H, J =9.0, 11.2 Hz); 3.87–3.80 (apparent ddd, 1H); 2.88 (m, 1H); 2.48–2.45 (complex m); 2.07 (s, 3H). ^{13}C NMR (D_2O): δ 176.1; 170.0; 157.1; 139.2; 129.5; 69.4; 56.2; 50.9; 30.3; 22.2.

Example 33

Synthesis of 102: A solution of azido allyl ether 6 (24 mg, 0.082 mmol) in ethanol (1 mL) was treated with hydrogen gas (1 atm) over Lindlar's catalyst (30 mg) for 1.5 h. The reaction mixture was filtered through a celite pad and washed with hot ethanol. Concentration in vacuo gave a pale solid which was dissolved in THF (1.5 mL) and treated with aqueous KOH (246 μL of a 0.50M solution). After stirring at ambient temperature for 2 h the reaction was acidified to pH=4.0 with Amberlite IR-120 (plus) acidic resin, filtered and washed with ethanol and H_2O . Concentration in vacuo gave an orange solid which was purified by a C_{18} column chromatography eluting with H_2O . Fractions containing the product were pooled and lyophilized to give a 2 to 1 mixture of 102 and the fully saturated compound 103 as a white powder.

^1H NMR data for compound 102: ^1H NMR (D_2O , 500 MHz): δ : 7.85 (s, 1H); 4.29 (br d, 1H, J =9.2 Hz); 4.16 (dd, 1H, J =11.6, 11.6 Hz); 3.78–3.72 (m, 2H); 3.62 (apparent ddd, 1H); 2.95 (apparent dd, 1H); 2.58–2.52 (m, 1H); 2.11 (s, 3H); 1.58 (q, 2H, J =7.3 Hz); 0.91 (t, 3H, J =7.3 Hz).

Example 34

Synthesis of 115: A solution of amino acid 114 (10.7 mg, 0.038 mmol) in water (1.3 mL) cooled to 0° C. was adjusted to pH=9.0 with 1.0M NaOH. Benzyl formimidate hydrochloride (26 mg, 0.153 mmol) was then added in one portion and the reaction stirred between 0°–5° C. for 3 h while maintaining the pH between 8.5–9.0 with 1.0M NaOH. The reaction was then concentrated in vacuo and the residue applied to a C_{18} column and eluted with water. Fractions containing the product were pooled and lyophilized to give the formamidine carboxylic acid 115 (10 mg) as a white powder.

^1H NMR (D_2O , 300 MHz, mixture isomers): δ 87.83 (s, 1H); [6.46(s) & 6.43 (s); 1H total]; 4.83 (d, 1H, J =7.3 Hz); 4.73 (d, 1H, J =7.3 Hz); 4.50–4.35 (m, 1H); 4.10–4.05 (m, 1H); [4.03–3.95 (m) & 3.80–3.65 (m), 1H total]; 3.39 (s, 3H); 2.90–2.75 (m, 1H); 2.55–2.30 (m, 1H); [2.03 (s) & 2.01 (s, 3H total)].

Example 35

Compound 123: To a solution of alcohol 63 (5.842 g, 20.5 mmol) and DMAP (200 mg) in pyridine (40 mL) was added tosyl chloride (4.3 g, 22.6 mmol). The mixture was stirred at room temperature for 40 hrs. and pyridine was removed under reduced pressure. The reaction was quenched with water, and extracted with EtOAc (3 \times). The combined organic extracts were washed with water, brine, and dried over MgSO_4 . Purification by flash column chromatography (Hexanes/EtOAc=2/1) gave the tosylate (8.04 g, 89%): ^1H

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NMR (CDCl₃) δ7.84 (d, J=8.3 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H), 4.78 (m, 1H), 4.43 (m, 1H), 4.06 (m, 1H), 3.79 (s, 3H), 2.44 (s, 3H), 2.43–1.92 (m, 4H), 1.61–1.22 (m, 10H).

Example 36

Compound 124: To a solution of alcohol 123 (440 mg, 1.0 mmol) in pyridine (3 mL) was added POCl₃ (100 μL, 1.1 mmol). The mixture was stirred at room temperature for 12 hrs. and quenched with saturated NH₄Cl solution. The water phase was extracted with ether (3x). The combined ether layers were washed with water (2x), 2N HCl solution (2x), brine, and dried over MgSO₄. Purification by flash column chromatography (Hexane/EtOAc=2/1) gave a mixture of the desired product 124 and some impurity (350 mg, 83%, 2/1).

Example 37

Compound 1: To a solution of the known acetonide of methyl shikimate (877 mg, 3.85 mmol, "Tetrahedron Lett.", 26:21 (1985)) in dichloromethane (15 mL) at -10° C. was added methanesulfonyl chloride (330 μL, 4.23 mmol) followed by the dropwise addition of triethylamine (640 μL, 4.62 mmol). The solution was stirred at -10° C. for 1 h then at 0° C. for 2 h, at which time methanesulfonyl chloride (30 μL), triethylamine (64 μL) was added. After 1 h cold water was added, the organic phase was separated, washed with water, dried (MgSO₄), and evaporated. The crude product was chromatographed on silica gel (1/1-hexane/ethyl acetate) to provide mesylate 130 (1.1 g, 93%) as an oil. Mesylate 130 (990 mg, 3.2 mmol) was dissolved in tetrahydrofuran (5 mL) and was treated with 1M HCl (5 mL). The solution was stirred at room temperature for 19 h, diluted with water (5 mL) and stirred an additional 7 h. Evaporation of the organic solvent precipitated an oily residue which was extracted into ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated. Addition of CH₂Cl₂ to the crude residue precipitated a white solid which was filtered and washed with CH₂Cl₂ to afford diol 131 (323 mg, 38%). To a partial suspension of diol 131 (260 mg, 0.98 mmol) in THF (5 mL) at 0° C. was added DBU (154 μL, 1.03 mmol). The solution was stirred at 0° C. for 3 h and then was warmed to room temperature stirring for 5 h. The solvent was evaporated and the crude residue was partitioned between ethyl acetate (40 mL) and 5% citric acid (20 mL). The organic phase was washed with brine. Aqueous phases were back extracted with ethyl acetate (15 mL) and the combined organic extracts were dried (MgSO₄) and evaporated to afford the epoxide (117 mg, 70%) as a white solid which gave an ¹H NMR spectrum consistent with structure 1 prepared by literature method.

Example 38

Alcohol 51: To a solution of protected alcohol (PG=methoxymethyl) (342 mg, 1.15 mmol) in CH₂Cl₂ (10 mL) at 0° C. was added trifluoroacetic acid (8 mL). After 5 min at 0° C., the solution was stirred 1 h at room temperature and was evaporated. The crude product was purified on silica gel (ethyl acetate) to afford alcohol 51 (237 mg, 82%) as an oil: ¹H NMR (300 MHz, CDCl₃) δ2.11 (s, 3H), 2.45 (m, 1H), 2.97 (dd, 1H, J=3.8, 18.8), 3.66 (m, 2H), 3.78 (s, 3H), 4.40 (br s, 1H), 5.22 (br s, 1H), 6.19 (br s, 1H), 6.82 (m, 1H).

Example 39

Methyl ether 150: To a solution of alcohol 51 (46 mg, 0.18 mmol) and methyl iodide (56 μL, 0.90 mmol) in THF (0.7 mL) at 0° C. was added NaH as a 60% mineral oil dispersion

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(8 mg, 0.20 mmol). The solution was stirred at 0° C. for 2.5 h, and a second portion of NaH (2 mg) was added. After an additional 1 h at 0° C. and 4 h at room temperature the solution was cooled to 0° C. and 5% citric acid (0.5 mL) was added. The mixture was extracted with ethyl acetate (4×2 mL) and the combined organic extracts were dried (MgSO₄), and evaporated. Purification of the crude residue on silica gel (ethyl acetate) gave methyl ether 150 (12 mg, 25%) as a solid: ¹H NMR (300 MHz, CDCl₃) δ2.07 (s, 3H), 2.23–2.34 (m, 1H), 2.89 (app ddd, 1H), 3.43 (s, 3H), 3.58 (m, 1H), 3.78 (s, 3H), 4.13 (m, 1H), 4.40 (m, 1H), 5.73 (d, 1H, J=7.6), 6.89 (m, 1H).

Example 40

15 Amino acid 151: To a solution of methyl ether 150 (12 mg, 0.45 mmol) in THF (1 mL)/water (100 μL) was added polymer support Ph₃P (75 mg, 3 mmol P/g resin). The mixture was stirred at room temperature for 19 h. The resin was filtered, washed several times with THF and the combined filtrate and washings were evaporated to provide 8 mg of a crude residue. The residue was dissolved in THF (0.5 mL), and 0.5M KOH (132 μL)/water (250 μL) was added. The solution was stirred at room temperature for 1.25 h and the pH was adjusted to 3–4 with IR120 ion exchange resin. 20 The resin was filtered and was stirred with 1M HCl. After filtration, the resin was subjected to the same treatment with 1M HCl until the acidic washes no longer tested positive for amine with ninhydrin. The combined resin washings were 25 evaporated and the residue was purified on C-18 reverse phase silica eluting with water to afford after lyophilization, amino acid 151 (1.8 mg, 15%) as a white solid: ¹H NMR (300 MHz, D₂O) δ2.09 (s, 3H), 2.48–2.59 (app qt, 1H), 2.94 (dd, 1H, J=5.7, 17.4), 3.61 (m, 1H), 4.14–4.26 (m, 2H), 6.86 (br s, 1H).

Example 41

40 Amino acid allyl ether 153: To a solution of azide 6 (16 mg, 0.054 mmol) in THF (0.50 mL) and H₂O (35 μL) was 45 added polystyrene supported PPh₃ (50 mg). The reaction was stirred at ambient temperature for 24 h, filtered through a sintered glass funnel and washed with hot methanol. Concentration in vacuo gave the crude amino ester which was dissolved in THF (1.0 mL) and treated with aqueous KOH (220 μL of a 0.5M solution). After stirring at ambient 50 temperature for 2 h Amberlite IR-120 (plus) acidic resin was added until the solution attained pH=4.5. The resin was filtered and washed with ethanol and H₂O. Concentration in vacuo gave a pale orange solid which was purified by reverse phase C₁₈ chromatography using H₂O as an eluent. Fractions containing the desired product were pooled and lyophilized to give the amino acid as a white powder.

¹H NMR (D₂O, 300 MHz): δ6.51 (br t, 1H); 6.05–5.80 (m, 1H, —CH=, allyl); 5.36–5.24 (m, 2H, =CH₂, allyl); 4.35–4.25 (m, 1H); 4.25–4.05 (m, 2H, —CH₂—, allyl); 4.02–3.95 (m, 1H); 3.81–3.70 (m, 1H); 2.86–2.77 (apparent dd, 1H); 2.35–2.24 (complex m, 1H); 2.09 (s, 3H).

Example 42

60 Epoxide 161: MCPBA (690 mg) was added to a solution of olefin 160 (532 mg, 1.61 mmol, prepared by Example 14, crude mesylate was filtered through silica gel using 30% EtOAc/Hexanes prior to use) in dichloromethane (15 mL) cooled to 0° C. The mixture was warmed to room temperature and stirred overnight. The bulk of the solvent was removed under vacuum and the mixture diluted with ethyl acetate. The organic layer was washed with aqueous sodium

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bisulfite, saturated sodium bicarbonate, brine and dried over $MgSO_4$. Concentration in vacuo followed by flash column chromatography of the residue (30% hexanes in ethyl acetate) gave 437 mg (78%) of 161 as a pale oil.

1H NMR ($CDCl_3$, 300 MHz): [1:1 mixture of diastereomers] δ [4.75 (dd, $J=3.9, 8.2$ Hz) & 4.71 (dd, $J=3.9, 8.4$ Hz), 1H total]; 4.37 (m, 1H); 4.25–4.00 (m, 2H); 3.78 (s, 3H); [3.68 (dd, $J=5.7, 11.7$ Hz) & 3.51 (dd, $J=6.6, 11.7$ Hz), 1H total]; [3.17 (s) & 3.16 (s), 3H total]; [2.99 (m) & 2.93 (m), 1H total]; [2.83 (t, $J=4.1$ Hz) & 2.82 (t, $J=4.5$ Hz), 1H total]; 2.70–2.60 (m, 1H); 2.45–2.30 (m, 1H).

Example 43

Diol 162: The epoxide 161 (437 mg, 1.23 mmol) was gently refluxed for 1 h in THF (20 mL) and H_2O (10 mL) containing 5 drops of 70% $HClO_4$. Solid $NaHCO_3$ was added and the mixture concentrated in vacuo. The residue was dissolved in EtOAc, washed with brine and dried. Concentration in vacuo gave the crude diol 162 as a pale oil in quantitative yield. Used without any purification for the next reaction.

Example 44

Aldehyde 163: Oxidation of diol 162 was carried out according to the procedure of Vo-Quang and co-workers, "Synthesis", 68 (1988). To a slurry of silica gel (4.3 g) in dichloromethane (30 mL) was added a solution of $NaIO_4$ (4.4 mL of a 0.65M aqueous solution). To this slurry was added a solution of the crude diol 162 (520 mg) in EtOAc (5 mL) and dichloromethane (15 mL). After 1 h the solids were filtered and washed with 20% hexanes/EtOAc. Concentration gave an oily residue which was dissolved in EtOAc and dried over $MgSO_4$. Concentration in vacuo gave the aldehyde 163 as a pale oil which was used immediately for the next reaction.

1H NMR ($CDCl_3$, 300 MHz): 89.69 (s, 1H); 6.98 (m, 1H); 4.72 (dd, 1H, $J=3.7, 9.1$ Hz); 4.53 (d, 1H, $J=18.3$ Hz); 4.45 (d, 1H, $J=18.3$ Hz); 4.31 (m, 1H); 4.26–4.18 (m, 1H); 3.79 (s, 3H); 3.19 (s, 3H); 3.05 (dd, 1H, $J=5.7, 18.6$ Hz); 2.20–2.45 (m, 1H).

Example 45

Alcohol 164: The crude aldehyde 163 was treated with $NaCNBH_3$ according to the procedure of Borch and co-workers, "J. Amer. Chem. Soc.", 93:2897 (1971) to give 269 mg (65%) of the alcohol 164 after flash chromatography (40% hexanes in ethyl acetate).

1H NMR ($CDCl_3$, 300 MHz): 86.91 (m, 1H); 4.75 (dd, 1H, $J=3.9, 8.7$ Hz); 4.34 (br t, 1H, $J=4.1$ Hz); 4.25–4.15 (m, 1H); 3.85–3.70 (m, 4H); 3.77 (s, 3H); 3.16 (s, 3H); 2.95 (dd, 1H, $J=5.7, 18.6$ Hz); 2.37 (dd, 1H, $J=7.1, 18.6$ Hz); 2.26 (br s, 1H).

Example 46

Aziridine 165: The alcohol 164 (208 mg, 0.62 mmol) was acetylated in the usual manner (AcCl, pyridine, dichloromethane, cat. DMAP) to give the acetate (241 mg, 100%). The crude acetate (202 mg, 0.54 mmol) was treated at room temperature with Ph_3P (155 mg) in THF (12 mL) for 2 h. H_2O (1.1 mL) and triethylamine (224 μ L) were then added and the solution stirred overnight. The reaction mixture was concentrated and the residue partitioned between ethyl acetate and saturated bicarbonate/brine. The organic layer was dried, concentrated in vacuo and purified by flash chromatography (10% MeOH in EtOAc) to give 125 mg (90%) of aziridine 165 as a white solid.

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1H NMR ($CDCl_3$, 300 MHz): 86.80 (m, 1H); 4.44 (br s, 1H); 4.23 (t, 2H, $J=4.8$ Hz); 3.82–3.65 (m, 2H); 3.74 (s, 3H); 2.85 (br d, 1H, $J=19.2$ Hz); 2.65–2.40 (m, 3H); 2.09 (s, 3H); 1.25 (br s, 1H).

Example 47

N-Boc aziridine 166: Boc anhydride (113 mg, 0.52 mmol) was added to a solution of aziridine 165 (125 mg, 0.49 mmol), triethylamine (70 μ L), DMAP (cat. amount) in dichloromethane (7 mL). After 1 h the reaction was concentrated and the residue subjected to flash chromatography (40% EtOAc in hexanes) to give 154 mg (88%) of the N Boc aziridine 166 as a pale oil.

1H NMR ($CDCl_3$, 300 MHz): 86.82 (m, 1H); 4.47 (br m, 1H); 4.23 (t, 2H, $J=4.7$ Hz); 3.81 (t, 2H, $J=4.7$ Hz); 3.75 (s, 3H); 3.00 (br d, 1H, $J=18.0$ Hz); 2.90–2.85 (m, 2H); 2.65–2.55 (m, 1H); 2.10 (s, 3H); 1.44 (s, 9H).

Example 48

Azido ester 167: Aziridine 166 (154 mg, 0.43 mmol), sodium azide (216 mg), and ammonium chloride (223 mg) was heated at 100°C. in DMF (5 mL) for 18 h. The cooled reaction mixture was partitioned between ethyl ether and brine. The ether layer was washed with H_2O , brine and dried over $MgSO_4$. Concentration gave a crude residue which was treated with 40% TFA in dichloromethane at room temperature. After 2 h the reaction was concentrated in vacuo to give a pale oil which was passed through a short column of silica gel eluting with EtOAc. The product was then acylated in the usual manner (AcCl, pyridine, dichloromethane, cat. DMAP) to give the azido ester 167 as a pale yellow oil 16 mg (11% for 3 steps) after flash chromatography (5% MeOH in chloroform).

1H NMR ($CDCl_3$, 300 MHz): 86.85 (m, 1H); 5.80 (br d, 1H, $J=7.8$ Hz); 4.55 (m, 1H); 4.25–4.10 (m, 3H); 3.90–3.85 (m, 2H); 3.78 (s, 3H); 3.55 (m, 1H); 2.90 (dd, 1H, $J=5.4, 17.0$ Hz); 2.45–2.25 (m, 1H); 2.10 (s, 3H); 2.05 (s, 3H).

Example 49

Amino acid 168: To a solution of ester 167 (16 mg, 0.047 mmol) in THF (1 mL) cooled to 0°C. was added aq. KOH (208 μ L of a 0.476M solution). The reaction was then warmed to room temperature and stirred for 2 h. The reaction was then acidified to pH=4.0 with Amberlite IR-120 (plus) acidic resin. The resin was then filtered and washed with ethanol and H_2O . Concentration in vacuo gave a 14 mg (100%) of the azido carboxylic acid as a white solid. The azido acid was dissolved in ethanol (2 mL) and treated with hydrogen gas (1 atm) over Lindlar's catalyst (15 mg) for 16 h according to the procedure of Corey and co-workers, "Synthesis", 590 (1975). The reaction mixture was filtered through a celite pad and washed with hot ethanol and H_2O . Concentration in vacuo gave a pale orange solid which was purified by a C_{18} column chromatography eluting with H_2O . The fractions containing the product were pooled and lyophilized to give 9.8 mg of 168 as a white powder.

1H NMR (D_2O , 500 MHz): δ : 6.53 (br s, 1H); 4.28 (br m, 1H); 4.08 (dd, 1H, $J=11.0, 11.0$ Hz); 3.80–3.65 (complex m, 4H); 3.44 (m, 1H); 2.84 (apparent dd, 1H); 2.46–2.39 (complex m, 1H); 2.08 (s, 3H).

Example 50

Epoxy MOM ether 19 (PG=methoxymethyl): Prepared in 74% from epoxy alcohol 1 according to the procedure of Mordini and co-workers, "J. Org. Chem.", 59:4784 (1994).

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¹H NMR (CDCl₃, 300 MHz): δ 6.73 (m, 1H); 4.87 (s, 2H); 4.59 (t, 1H, J=2.4 Hz); 3.76 (s, 3H); 3.57 (m, 1H); 3.50–3.40 (m, 1H); 3.48 (s, 3H); 3.10 (d, J=19.5 Hz); 2.45 (m, 1H).

Example 51

Aziridine 170: Prepared in 77% overall from epoxide 19 (PG=methoxymethyl) according to the general protocol described in Examples 3 and 4: ¹H NMR (CDCl₃, 300 MHz): δ 6.85 (m, 1H); 4.78 (s, 2H); 4.54 (m, 1H); 3.73 (s, 3H); 3.41 (s, 3H); 2.87 (d, 1H, J=18.9 Hz); 2.70–2.45 (m, 3H).

Example 52

Azido ester 22 (PG=methoxymethyl): The aziridine 170 (329 mg, 1.54 mmol), NaN₃ (446 mg) and NH₄Cl (151 mg) was heated at 65° C. in DMF (20 mL) for 18 h. The cooled reaction mixture was partitioned between ethyl ether and brine. The ether layer was washed with H₂O, brine and dried over MgSO₄. Concentration in vacuo gave the crude azido amine as a pale oil which was taken up in CH₂Cl₂ (15 mL) and treated with pyridine (4 mL) and AcCl (150 μL). Aqueous work up followed by flash chromatography of the residue gave 350 mg (76%) of azido ester 22 (PG=methoxymethyl) as a pale oil.

¹H NMR (CDCl₃, 300 MHz): δ 6.78 (s, 1H); 6.39 (br d, 1H, J=7.8 Hz); 4.72 (d, 1H, J=6.9 Hz); 4.66 (d, 1H, J=6.9 Hz); 4.53 (br d, 1H, J=8.4 Hz); 4.00–3.90 (m, 1H); 3.80–3.65 (m, 1H); 3.75 (s, 3H); 3.37 (s, 3H); 2.85 (dd, 1H, J=5.4, 17.7 Hz); 2.35–2.20 (m, 1H); 2.04 (s, 3H).

Example 53

Amino acid 114: The azide 22 (PG=methoxymethyl) (39 mg, 0.131 mmol) was treated with hydrogen gas at 1 atmosphere over Lindlar's catalyst (39 mg) in ethanol for 2.5 h according to the procedure of Corey and coworkers, "Synthesis", 590 (1975). The reaction mixture was filtered through a celite pad, washed with hot ethanol and concentrated to give the crude amine 33 mg (92%) as a pale foam. The amine in THF (1 mL) was treated with aq. KOH (380 μL of a 0.476M solution). After 1 h the reaction was acidified to pH=4.0 with Amberlite IR-120 (plus) acidic resin. The resin was then filtered, washed with H₂O and concentrated to give a pale solid which was purified by a C₁₈ column chromatography eluting with H₂O. The fractions containing the product were pooled and lyophilized to give 20 mg of 114 as a white powder.

¹H NMR (D₂O, 300 MHz): δ 6.65 (s, 1H); 4.87 (d, 1H, J=7.5 Hz); 4.76 (d, 1H, J=7.5 Hz); 4.47 (br d, 1H, J=8.7 Hz); 4.16 (dd, 1H, J=11.4, 11.4 Hz); 3.70–3.55 (m, 1H); 3.43 (s, 3H); 2.95 (dd, 1H, J=5.7, 17.4 Hz); 2.60–2.45 (m, 1H); 2.11 (s, 3H).

Example 54

Amino acid 171: To solid amino acid 114 (4 mg, 0.015 mmol) was added 40% TFA in CH₂Cl₂ (1 mL, cooled to 0° C. prior to addition). After stirring at room temperature for 1.5 h the reaction mixture was concentrated to give a white foam. Co-evaporation from H₂O several times followed by lyophilization gave a white solid, 5.5 mg of 117 as the TFA salt.

¹H NMR (D₂O, 300 MHz): δ 6.85 (m, 1H); 4.45 (m, 1H); 4.05 (dd, 1H, J=11.4, 11.4 Hz); 3.65–3.55 (m, 1H); 3.00–2.90 (m, 1H); 2.60–2.45 (m, 1H); 2.09 (s, 3H).

Example 55

Acetonide 180: To a suspension of shikimic acid (25 g, 144 mmol, Aldrich) in methanol (300 mL) was added

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p-toluenesulfonic acid (274 mg, 1.44 mmol, 1 mol %) and the mixture was heated to reflux for 2 h. After adding more p-toluenesulfonic acid (1 mol %) the reaction was refluxed for 26 h and was evaporated. The crude methyl ester (28.17 g) was suspended in acetone (300 mL) and was treated with dimethoxypyropane (35 mL, 288 mmol) and was stirred at room temperature for 6 h and then was evaporated. The crude product was dissolved in ethyl acetate (400 mL) and was washed with saturated NaHCO₃ (3×125 mL) and saturated NaCl. The organic phase was dried (MgSO₄), filtered, and evaporated to afford crude acetonide 180 (~2.94 g) which was used directly: ¹H NMR (CDCl₃) δ 6.91 (t, 1H, J=1.1), 4.74 (t, 1H, J=4.8), 4.11 (t, 1H, J=6.9), 3.90 (m, 1H), 2.79 (dd, 1H, J=4.5, 17.4), 2.25 (m, 2H), 1.44 (s, 3H), 1.40 (s, 3H).

Example 56

Mesylate 130: To a solution of acetonide 180 (29.4 g, 141 mmol) in CH₂Cl₂ (250 mL) at 0° C. was added triethylamine (29.5 mL, 212 mmol) followed by the addition of methanesulfonyl chloride (13.6 mL, 176 mmol) over a period of 10 min. The reaction was stirred at 0° C. for 1 h and ice cold water (250 mL) was added. After transfer to a separatory funnel, the organic phase was washed with water, 5% citric acid (300 mL), saturated NaHCO₃ (300 mL) and was dried (MgSO₄), filtered, and evaporated. The crude product was filtered through a short plug of silica gel on a fritted glass funnel eluting with ethyl acetate. The filtrate was evaporated to afford mesylate 130 (39.5 g, 91%) as a viscous oil which was used directly in the next step: ¹H NMR (CDCl₃) δ 6.96 (m, 1H), 4.80 (m, 2H), 4.28 (dd, 1H, J=6.6, 7.5), 3.79 (s, 3H), 3.12 (s, 3H), 3.01 (dd, 1H, J=5, 17.7), 2.56–2.46 (m, 1H).

Example 57

Diol 131: To a solution of mesylate 130 (35.85 g, 117 mmol) in methanol (500 mL) was added p-toluenesulfonic acid (1.11 g, 5.85 mmol, 5 mol %) and the solution was refluxed for 1.5 h and was evaporated. The residue was redissolved in methanol (500 mL) and was refluxed an additional 4 h. The solvent was evaporated and the crude oil was triturated with diethyl ether (250 mL). After completing the crystallization overnight at 0° C., the solid was filtered and was washed with cold diethyl ether, and dried to afford diol 131 (24.76 g) as a white solid. Evaporation of the filtrate and crystallization of the residue from methanol/diethyl ether gave an additional 1.55 g. Obtained 26.3 g (85%) of diol 131: ¹H NMR (CD₃OD) δ 6.83 (m, 1H), 4.86 (m, 1H), 4.37 (t, 1H, J=4.2), 3.87 (dd, 1H, J=4.2, 8.4), 3.75 (s, 3H), 3.13 (s, 3H), 2.98–2.90 (m, 1H), 2.53–2.43 (m, 1H).

Example 58

Epoxy alcohol 1: A suspension of diol 131 (20.78 g, 78 mmol) in tetrahydrofuran (400 mL) at 0° C. was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (11.7 mL, 78 mmol) and was stirred at room temperature for 9 h at which time the reaction was complete. The reaction was evaporated and the crude residue was dissolved in CH₂Cl₂ (200 mL) and was washed with saturated NaCl (300 mL). The aqueous phase was extracted with CH₂Cl₂ (2×200 mL). The combined organic extracts were dried (MgSO₄), filtered, and evaporated. The crude product was purified on silica gel (ethyl acetate) to afford epoxy alcohol 1 (12 g, 90%) as a white solid whose ¹H NMR spectrum was consistent with that reported in the literature: McGowan, D. A.; Berchtold, G. A., "J. Org. Chem.", 46:2381 (1981).

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Example 59

Methoxymethyl ether 22 (PG=methoxymethyl): To a solution of epoxy alcohol 1 (4 g, 23.5 mmol) in CH_2Cl_2 (100 mL) was added N,N'-diisopropylethylamine (12.3 mL, 70.5 mmol) followed by chloromethyl methyl ether (3.6 mL, 47 mmol, distilled from tech. grade). The solution was refluxed for 3.5 h and the solvent was evaporated. The residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The aqueous phase was extracted with ethyl acetate (100 mL). The combined organic extracts were washed with saturated NaCl (100 mL), dried (MgSO_4), filtered, and evaporated to afford 4.9 g of a solid residue which was of suitable purity to use directly in the next step: mp 62°–65° (crude); mp 64°–66° C. (diethyl ether/hexane); ^1H NMR (CDCl_3) δ6.73 (m, 1H), 4.87 (s, 2H), 4.59 (m, 1H), 3.75 (s, 3H), 3.57 (m, 1H), 3.48 (m overlapping s, 4H), 3.07 (dd, 1H, J =1.2, 19.8), 2.47 (dq, 1H, J =2.7, 19.5).

Example 60

Alcohol 181: To a solution of methoxymethyl ether 22 (PG=methoxymethyl) (4.9 g, 22.9 mmol) in 8/1-MeOH/H₂O (175 mL, v/v) was added sodium azide (7.44 g, 114.5 mmol) and ammonium chloride (2.69 g, 50.4 mmol) and the mixture was refluxed for 15 h. The reaction was diluted with water (75 mL) to dissolve precipitated salts and the solution was concentrated to remove methanol. The resulting aqueous phase containing a precipitated oily residue was diluted to a volume of 200 mL with water and was extracted with ethyl acetate (3×100 mL). The combined organic extracts were washed with saturated NaCl (100 mL), dried (MgSO_4), filtered and evaporated. The crude was purified on silica gel (1/1-hexane/ethyl acetate) to afford alcohol 181 (5.09 g, 86%) as a pale yellow oil. Subsequent preparations of alcohol 181 provided material which was of sufficient purity to use in the next step without further purification: ^1H NMR (CDCl_3) δ6.86 (m, 1H), 4.79 (s, 2H), 4.31 (br t, 1H, J =4.2), 3.90–3.75, 3.77 (m overlapping s, 5H); 3.43 (s, 3H), 2.92 (d, 1H, J =6.6), 2.87 (dd, 1H, J =5.4, 18.6), 2.21–2.30 (m, 1H).

Example 61

Mesylate 184: To a solution of alcohol 181 (6.47 g, 25.2 mmol) in CH_2Cl_2 (100 mL) at 0° C. was added first triethyl amine (4.4 mL, 31.5 mmol) then methanesulfonyl chloride (2.14 mL, 27.7 mmol). The reaction was stirred at 0° C. for 45 min then was warmed to room temperature stirring for 15 min. The reaction was evaporated and the residue was partitioned between ethyl acetate (200 mL) and water (100 mL). The organic phase was washed with water (100 mL), saturated NaHCO_3 (100 mL), saturated NaCl (100 mL). The water washes were extracted with a single portion of ethyl acetate which was washed with the same NaHCO_3 /NaCl solutions. The combined organic extracts were dried (MgSO_4), filtered, and evaporated. The crude product was of suitable purity to be used directly in the next step: ^1H NMR (CDCl_3) δ6.85 (m, 1H), 4.82 (d, 1H, J =6.9), 4.73 (d, 1H, J =6.9), 4.67 (dd, 1H, J =3.9, 9.0), 4.53 (br t, 1H, J =4.2), 3.78 (s, 3H), 3.41 (s, 3H), 3.15 (s, 3H), 2.98 (dd, 1H, J =6.0, 18.6), 2.37 (m, 1H); ^{13}C NMR (CDCl_3) δ165.6, 134.3, 129.6, 96.5, 78.4, 69.6, 55.8, 55.7, 52.1, 38.2, 29.1.

Example 62

Aziridine 170: To a solution of mesylate 184 (8.56 g, 25 mmol) in THF (150 mL) at 0° C. was added Ph_3P (8.2 g, 31 mmol), initially adding a third of the amount while cooling and then after removing the ice bath adding the remainder of

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the Ph_3P over a period of 10–15 min. After complete addition of the Ph_3P the reaction was stirred at room temperature for 3 h with the formation of a white precipitate. To this suspension was added triethyl amine (5.2 mL, 37.5 mmol) and water (10 mL) and the mixture was stirred at room temperature for 12 h. The reaction was concentrated to remove THF and the residue was partitioned between CH_2Cl_2 (200 mL) and saturated NaCl (200 mL). The aqueous phase was extracted with several portions of CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to afford a crude product which was purified on silica gel (10% MeOH/EtOAc) to afford aziridine 170 (4.18 g, 78%) as an oil which typically contained trace amounts of triphenylphosphine oxide impurity: ^1H NMR (CDCl_3) δ6.81 (m, 1H), 4.78 (s, 2H), 4.54 (m, 1H), 3.73 (s, 3H), 3.41 (s, 3H), 2.87 (app dd, 1H), 2.64 (br s, 1H), 2.56–2.47 (m, 2H), NH signal was not apparent; ^{13}C NMR (CDCl_3) δ166.9, 132.5, 128.0, 95.9, 69.5, 55.2, 51.6, 31.1, 27.7, 24.1.

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Example 63

Amine 182: To a solution of aziridine 170 (3.2 g, 15 mmol) in DMF (30 mL) was applied a vacuum on a rotary evaporator (40° C.) for several minutes to degas the solution. 25 To the solution was added sodium azide (4.9 g, 75 mmol) and ammonium chloride (1.6 g, 30 mmol) and the mixture was heated at 65°–70° C. for 21 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (~100 mL) and was filtered. The filtrate was evaporated and the residue was partitioned between diethyl ether (100 mL) and saturated NaCl (100 mL). The organic phase was washed again with saturated NaCl (100 mL), dried (MgSO_4), filtered, and was evaporated. Additional crude product was obtained from the aqueous washings by extraction with ethyl acetate and treated in the same manner as described above. 30 The crude product was purified on silica gel (5%MeOH/ CH_2Cl_2) to afford amine 182 (2.95 g) as an oil which contained a small amount of triphenylphosphine oxide impurity from the previous step: ^1H NMR (CDCl_3) δ6.82 (t, 1H, J =2.3), 4.81 (d, 1H, J =7.2), 4.77 (d, 1H, J =6.9), 4.09–4.04 (m, 1H), 3.76 (s, 3H), 3.47 and 3.44 (m overlapping s, 4H), 2.94–2.86 (m, 2H), 2.36–2.24 (m, 1H); ^{13}C NMR (CDCl_3) δ165.9, 137.3, 128.2, 96.5, 79.3, 61.5, 55.7, 55.6, 51.9, 29.5.

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Example 64

N-Trityl aziridine 183: Amine 182 (2.59 g, 10.2 mmol) was dissolved in 5% HCl/MeOH (30 mL) and the solution 50 was stirred for 3 h at room temperature. Additional 5% HCl/MeOH (10 mL) was added stirring 1 h and the solvent was evaporated to afford 2.52 g of the HCl salt as a tan solid after high vacuum. To a suspension of the HCl salt in CH_2Cl_2 (50 mL) at 0° C. was added triethylamine (3.55 mL, 55.5 mmol) followed by the addition of solid trityl chloride (5.55 g, 12.8 mmol) in one portion. The mixture was stirred at 0° C. for 1 h and then was warmed to room temperature stirring for 2 h. The reaction was cooled to 0° C., triethylamine (3.6 mL, 25.5 mmol) was added and methane sulfonyl chloride (0.97 mL, 12.5 mmol) was added, stirring the resulting mixture for 1 h at 0° C. and for 22 h at room temperature. The reaction was evaporated and the residue was partitioned between diethyl ether (200 mL) and water (200 mL). The organic phase was washed with water (200 mL) and the combined aqueous phases were extracted with diethyl ether (200 mL). The combined organic extracts were washed with water (100 mL), saturated NaCl (200 mL) and

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were dried (Na_2SO_4), filtered, and evaporated. The crude product was purified on silica gel (1/1-hexane/ CH_2Cl_2) to afford N-trityl aziridine 183 (3.84 g, 86%) as a white foam: ^1H NMR (CDCl_3) δ 7.4–7.23 (m, 16H), 4.32 (m, 1H), 3.81 (s, 3H), 3.06 (dt, 1H, J =1.8, 17.1), 2.94–2.86 (m, 1H), 2.12 (m, 1H), 1.85 (t, 1H, J =5.0).

Example 65

Compound 190: A solution of N-trityl aziridine 183 (100 mg, 0.23 mmol), cyclohexanol (2 mL) and boron trifluoride etherate (42 μL , 0.35 mmol) was heated at 70° C. for 1.25 h and was evaporated. The residue was dissolved in pyridine (2 mL) and was treated with acetic anhydride (110 μL , 1.15 mmol) and catalytic DMAP. After stirring for 3 h at room temperature the reaction was evaporated. The residue was partitioned between ethyl acetate and 5% citric acid. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with saturated NaHCO_3 , and saturated NaCl. The organic phase was dried (MgSO_4), filtered, and evaporated. The crude product was purified on silica gel (1/1-hexane/ethyl acetate) to afford compound 190 (53 mg, 69%) as a solid: mp 105°–107° C. (ethyl acetate/hexane); ^1H NMR (CDCl_3) δ 6.78 (m, 1H), 6.11 (d, 1H, J =7.4), 4.61 (m, 1H), 4.32–4.23 (m, 1H), 3.76 (s, 3H), 3.44–3.28 (m, 2H), 2.85 (dd, 1H, J =5.7, 17.6), 2.28–2.17 (m, 1H), 2.04 (s, 3H), 1.88–1.19 (m, 10H).

Example 66

Compound 191: To a solution of compound 190 (49 mg, 0.15 mmol) in THF was added triphenylphosphine (57 mg, 0.22 mmol) and water (270 μL) and the solution was heated at 50° C. for 10 h. The reaction was evaporated and the residue was dissolved in ethyl acetate, dried (Na_2SO_4), filtered and evaporated. The crude product was purified on silica gel (1/1-methanol/ethyl acetate) to afford the amine (46 mg) as a pale yellow solid. To a solution of the amine in THF (1.5 mL) was added 1.039N KOH solution (217 μL) and water (200 μL). The mixture was stirred at room temperature for 1 h and was then cooled to 0° C. and acidified to pH 6–6.5 with IR 120 ion exchange resin. The resin was filtered, washed with methanol and the filtrate was evaporated. The solid residue was dissolved in water and was passed through a column (4×1 cm) of C-18 reverse phase silica gel eluting with water and then 2.5% acetonitrile/water. Product fractions were combined and evaporated and the residue was dissolved in water and lyophilized to afford amino acid 191 (28 mg) as a white solid: ^1H NMR (D_2O) δ 6.47 (br s, 1H), 4.80 (br d, 1H), 4.00 (dd, 1H, J =8.9, 11.6), 3.59–3.50 (m, 2H), 2.87 (dd, 1H, J =5.5, 17.2), 2.06 (s, 3H), 1.90–1.15 (series of m, 10H); Anal. Calcd for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_4\text{H}_2\text{O}$: C, 57.31; H, 8.34; N, 8.91. Found: C, 57.38; H, 8.09; N, 8.77.

Example 67

bis-Boc guanidino ester 201: Treated according to the procedure of Kim and Qian, "Tetrahedron Lett.", 34:7677 (1993). To a solution of amine 200 (529 mg, 1.97 mmol, prepared by the method of Example 109, bis-Boc thiourea (561 mg, 2.02 mmol) and Et_3N (930 μL) in dry DMF (5.0 mL) cooled to 0° C. was added HgCl_2 (593 mg, 2.18 mmol) in one portion. The heterogeneous reaction mixture was stirred for 45 min at 0° C. and then at room temperature for 15 min, after which the reaction was diluted with EtOAc and filtered through a pad of celite. Concentration in vacuo followed by flash chromatography of the residue on silica gel (10% hexanes in ethyl acetate) gave 904 mg (90%) of 201 as a pale oil.

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^1H NMR (CDCl_3 , 300 MHz): δ 11.39 (s, 1H); 8.63 (d, 1H, J =7.8 Hz); 6.89 (t, 1H, J =2.4 Hz); 6.46 (d, 1H, J =8.7 Hz); 4.43–4.32 (m, 1H); 4.27–4.17 (m, 1H); 4.13–4.06 (m, 1H); 3.77 (s, 3H); 3.67–3.59 (m, 1H); 2.83 (dd, 1H, J =5.1, 17.7 Hz); 2.45–2.33 (m, 1H); 1.95 (s, 3H); 1.65–1.50 (m, 2H); 1.45 (s, 18H); 0.90 (t, 3H, J =7.5 Hz).

Example 68

Carboxylic acid 202: To a solution of methyl ester 201 (904 mg, 1.77 mmol) in THF (10 mL) was added aqueous KOH (3.45 mL of a 1.039N solution). The reaction mixture was stirred at room temperature for 17 h, cooled to 0° C. and acidified to pH 4.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration in vacuo gave the free acid as a pale foam which was used without further purification in the next reaction.

Example 69

Guanidine carboxylic acid 203: To a solution of bis-Boc guanidinyl acid 202 (crude from previous reaction) in CH_2Cl_2 (40 mL) cooled to 0° C. was added neat trifluoroacetic acid (25 mL). The reaction mixture was stirred at 0° C. for 1 h and then at room temperature for 2 h. Concentration in vacuo gave a pale orange solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 495 mg (68%, 2 steps) of the guanidine carboxylic acid 203 as the trifluoroacetic acid salt.

^1H NMR (D_2O , 300 MHz): δ 6.66 (s, 1H); 4.29 (bd, 1H, J =9.0 Hz); 4.01 (dd, 1H, J =10.8, 10.8 Hz); 3.87–3.79 (m, 1H); 3.76–3.67 (m, 1H); 3.60–3.50 (m, 1H); 2.83 (dd, 1H, J =5.1, 17.4 Hz); 2.47–2.36 (m, 1H); 2.06 (s, 3H); 1.65–1.50 (m, 2H); 0.90 (t, 3H, J =7.2 Hz). Anal. Calcd for $\text{C}_{15}\text{H}_{23}\text{O}_6\text{N}_4\text{F}_3$: C, 43.69; H, 5.62; N, 13.59. Found: C, 43.29; H, 5.90; N, 13.78.

Example 70

Formamidine carboxylic acid 204: A solution of amino acid 102 (25 mg, 0.10 mmol, prepared by the method of Example 110) in water (500 μL) at 0°–5° C. was adjusted to pH 8.5 with 1.0N NaOH. Benzyl formimidate hydrochloride (45 mg, 0.26 mmol) was added in one portion and the reaction mixture was stirred for 3 h at this temperature while maintaining the pH at 8.5–9.0 with 1.0N NaOH. The reaction was then concentrated in vacuo and purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 4.0 mg (13%) of the formamidine carboxylic acid 204.

^1H NMR (D_2O , 300 MHz): δ 7.85 (s, 1H); 6.53 (bd, 1H, J =7.8 Hz); 4.32–4.25 (bm, 1H); 4.10–3.97 (m, 1H); 3.76–3.67 (m, 2H); 3.57–3.49 (m, 1H); 2.86–2.81 (m, 1H); 2.55–2.40 (m, 1H); 2.04 (s, 3H); 1.65–1.50 (m, 2H); 0.90 (t, 3H, J =7.4 Hz).

Example 71

Amino acid 206: To a solution of amino methyl ester 205 (84 mg, 0.331 mmol, prepared by Example 107) in THF (1.0 mL) was added aqueous KOH (481 μL of a 1.039N solution). The reaction mixture was stirred at room temperature for 2.5 h and acidified to pH 6.5 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration in vacuo gave the amino acid as a white solid which was purified by C₁₈ reverse

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phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 59 mg (74%) of the amino acid 206.

¹H NMR (^{CD}₃OD, 300 MHz): 86.60 (bd, 1H, J=1.8 Hz); 4.01–3.95 (m, 1H); 3.71–3.60 (m, 2H); 3.50–3.42 (m, 1H); 3.05–2.85 (m, 2H); 2.39–2.28 (m, 1H); 1.70–1.55 (m, 2H); 0.95 (t, 3H, J=7.5 Hz).

Example 72

Trifluoroacetamide 207: To a degassed solution of amino acid 206 (59 mg, 0.246 mmol) in dry methanol (1.0 mL) under argon was added Et₃N (35 μ L) followed by methyl trifluoroacetate (35 μ L). The reaction was stirred for one week at room temperature and concentrated. Analysis by ¹H NMR showed that reaction was 40% complete. The crude reaction product was redissolved in dry methanol (1.0 mL), methyl trifluoroacetate (1.0 mL) and Et₃N (0.5 mL) and stirred at room temperature for 5 days. The reaction was then concentrated in vacuo and dissolved in 50% aqueous THF (2.0 mL), acidified to pH 4 with Amberlite IR-120 (H⁺) acidic resin and filtered. Concentration gave the crude trifluoroacetamide carboxylic acid which was used without further purification for the next reaction.

Example 73

Amino acid 208: A solution of azide 207 (crude from previous reaction) in THF (2.0 mL) and water (160 μ L) was treated with polymer supported triphenyl phosphine (225 mg) at room temperature. After stirring for 20 h the polymer was filtered and washed with methanol. Concentration in vacuo gave a pale solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 6.5 mg (9%) of the trifluoroacetamide amino acid 208.

¹H NMR (D₂O, 300 MHz): 86.59 (bs, 1H); 4.40–4.30 (m, 1H); 4.26 (t, 1H, J=10.1 Hz); 3.80–3.66 (m, 2H); 3.56–3.47 (m, 1H); 2.96 (bdd, 1H, J=5.4, 17.7 Hz); 2.58–2.45 (m, 1H); 1.62–1.50 (m, 2H); 0.89 (t, 3H, J=7.5 Hz).

Example 74

Methylsulfonamido methyl ester 209: Methanesulfonyl chloride (19 μ L) was added to a solution of amine 205 (58 mg, 0.23 mmol, prepared by Example 107), Et₃N (97 μ L) and a catalytic amount of DMAP (few crystals) in CH₂Cl₂ (1.0 mL) at 0° C. After 30 min the reaction mixture was warmed to room temperature and stirred for an additional 1 h. Concentration in vacuo followed by flash chromatography of the residue on silica gel (50% hexanes in ethyl acetate) gave 61 mg (79%) of the sulfonamide 209.

¹H NMR (CDCl₃, 300 MHz): 86.87 (t, 1H, J=2.3 Hz); 5.08 (d, 1H, J=7.5 Hz); 4.03–3.90 (m, 1H); 3.78 (s, 3H); 3.75–3.45 (m, 4H); 3.14 (s, 3H); 2.95 (dd, 1H, J=5.2, 17.3 Hz); 2.42–2.30 (m, 1H); 1.75–1.55 (m, 2H); 0.95 (t, 3H, J=7.5 Hz).

Example 75

Amino ester 210: A solution of azide 209 (61 mg, 0.183 mmol) in THF (2.0 mL) and water (118 μ L) was treated with polymer supported triphenyl phosphine (170 mg) at room temperature. After stirring for 17.5 h the polymer was filtered and washed with methanol. Concentration in vacuo followed by flash chromatography of the residue through a short silica gel column (100% methanol) gave 45 mg (80%) of the amino ester 210 as a pale foam.

¹H NMR (CDCl₃, 300 MHz): 86.85 (s, 1H); 3.94 (bd, 1H, J=7.8 Hz); 3.77 (s, 3H); 3.74–3.60 (m, 2H); 3.55–3.45 (m,

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1H); 3.25–3.15 (m, 1H); 3.11 (s, 3H); 2.94–2.85 (m, 1H); 2.85 (bs, 2H); 2.22–2.10 (m, 1H); 1.70–1.56 (m, 2H); 0.94 (t, 3H, J=7.5 Hz).

Example 76

Amino acid 211: A solution of methyl ester 210 (21 mg, 0.069 mmol) in THF (200 μ L) was treated with aqueous KOH (135 μ L of a 1.039N solution). The reaction mixture was stirred at room temperature for 40 min and neutralized to pH 7.0 with Amberlite IR-120 (H⁺) acidic resin. The resin was filtered and washed with water and methanol. Concentration in vacuo gave the amino acid as a pale solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 3.5 mg (17%) of the amino acid 211.

¹H NMR (D₂O, 300 MHz): 86.60 (d, 1H, J=1.8 Hz); 4.30–4.20 (m, 1H); 3.84–3.75 (m, 1H); 3.68–3.58 (m, 1H); 3.60–3.40 (m, 2H); 3.20 (s, 3H); 2.96–2.88 (m, 1H); 2.55–2.45 (m, 1H); 1.72–1.59 (m, 2H); 0.93 (t, 3H, J=7.4 Hz).

Example 77

Bis-Boc guanidino ester 212: Treated according to the procedure of Kim and Qian, "Tetrahedron Lett." 34:7677 (1993). To a solution of amine 210 (31 mg, 0.101 mmol), bis-Boc thiourea (28.5 mg, 0.103 mmol) and Et₃N (47 μ L) in dry DMF (203 μ L) cooled to 0° C. was added HgCl₂ (30 mg, 0.11 mmol) in one portion. The heterogeneous reaction mixture was stirred for 30 min at 0° C. and then at room temperature for 30 min, after which the reaction was diluted with EtOAc and filtered through a pad of celite. Concentration in vacuo followed by flash chromatography of the residue on silica gel (40% hexanes in ethyl acetate) gave 49 mg (89%) of 212 as a pale oil.

¹H NMR (CDCl₃, 300 MHz): 811.47 (s, 1H); 8.66 (d, 1H, J=8.4 Hz); 6.87 (s, 1H); 6.01 (bs, 1H); 4.50–4.35 (m, 1H); 4.04 (bd, 1H, J=8.4 Hz); 3.76 (s, 3H); 3.70–3.60 (m, 1H); 3.53–3.45 (m, 2H); 3.02 (s, 3H); 2.85 (dd, 1H, J=5.3, 17.3 Hz); 2.42–2.30 (m, 1H); 1.66–1.55 (m, 2H); 1.49 (s, 9H); 1.48 (s, 9H); 0.93 (t, 3H, J=7.3 Hz).

Example 78

Carboxylic acid 213: To a solution of methyl ester 212 (49 mg, 0.090 mmol) in THF (1.0 mL) was added aqueous KOH (260 μ L of a 1.039N solution). The reaction mixture was stirred at room temperature for 16 h, cooled to 0° C. and acidified to pH 4.0 with Amberlite IR-120 (H⁺) acidic resin. The resin was filtered and washed with water and methanol. Concentration in vacuo gave the free acid as a pale foam which was used without further purification in the next reaction.

Example 79

Guanidine carboxylic acid 214: To a solution of bis-Boc guanidyl acid 213 (crude from previous reaction) in CH₂Cl₂ (2.0 mL) cooled to 0° C. was added neat trifluoroacetic acid (2.0 mL). The reaction mixture was stirred at 0° C. for 1 h and then at room temperature for 1 h. Concentration in vacuo gave a pale orange solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 10 mg (25%, 2 steps) of the guanidine carboxylic acid 214.

¹H NMR (D₂O, 300 MHz): 86.60 (bs, 1H); 4.22 (bd, 1H, J=9.0 Hz); 3.82–3.66 (m, 2H); 3.65–3.54 (m, 1H); 3.43 (bt,

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1H, J=9.9 Hz); 3.15 (s, 3H); 2.82 (dd, 1H, J=5.0, 17.5 Hz); 2.48–2.30 (m, 1H); 1.71–1.58 (m, 2H); 0.93 (t, 3H, J=7.3 Hz).

Example 80

Propionamide methyl ester 215: Propionyl chloride (96 μ L, 1.1 mmol) was added to a solution of amine 205 (178 mg, 0.70 mmol, prepared by Example 107) and pyridine (1.5 mL) in CH_2Cl_2 (2.0 mL) cooled to 0° C. After 30 min at 0° C. the reaction was concentrated and partitioned between ethyl acetate and brine. The organic layer was separated and washed sequentially with saturated sodium bicarbonate, brine and dried over MgSO_4 . Concentration in vacuo followed by flash chromatography of the residue on silica gel (40% hexanes in ethyl acetate) gave 186 mg (86%) of the propionamide methyl ester 215 as a pale yellow solid.

¹H NMR (CDCl_3 , 300 MHz): δ 8.68 (t, 1H, J=2.3 Hz); 5.72 (bd, 1H, J=7.8 Hz); 4.52–4.49 (m, 1H); 4.25–4.15 (m, 1H); 3.77 (s, 3H); 3.65–3.37 (complex m, 3H); 2.87 (dd, 1H, J=5.7, 17.7 Hz); 2.28 (q, 2H, J=7.5 Hz); 2.25–2.20 (m, 1H); 1.65–1.50 (m, 2H); 1.19 (t, 3H, J=7.5 Hz); 0.92 (t, 3H, J=7.5 Hz).

Example 81

Amino methyl ester 216: A solution of azide 215 (186 mg, 0.60 mmol) in THF (5.0 mL) and water (400 μ L) was treated with polymer supported triphenyl phosphine (560 mg) at room temperature. After stirring for 21 h the polymer was filtered and washed with methanol. Concentration in vacuo gave the crude amino ester 216 which was used without any further purification for the next step.

Example 82

Amino acid 217: A solution of methyl ester 216 (crude from previous reaction) in THF (500 μ L) was treated with aqueous KOH (866 μ L of a 1.039N solution). The reaction mixture was stirred at room temperature for 3 h and neutralized to pH 7.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration in vacuo gave the amino acid as a pale solid which was purified by C_{18} reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 49 mg (31% 2 steps) of the amino acid 217.

¹H NMR (D_2O , 300 MHz): δ 8.54 (s, 1H); 4.25 (bd, 1H, J=8.7 Hz); 4.13 (dd, 1H, J=9.0, 11.3 Hz); 3.74–3.60 (m, 1H); 3.61–3.40 (m, 2H); 2.85 (dd, 1H, J=5.9, 17.1 Hz); 2.55–2.40 (m, 1H); 2.35 (q, 2H, J=7.5 Hz); 1.65–1.45 (m, 2H); 1.13 (t, 3H, J=7.5 Hz); 0.88 (t, 3H, J=7.5 Hz).

Example 83

(mono methyl) bis-Boc guanidino ester 218: To a solution of amine 200 (51 mg, 0.19 mmol) and mono methyl bis-Boc thiourea (36 mg, 0.19 mmol) in dry DMF (1.0 mL), was added 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (38 mg) and Et_3N (56 μ L) at room temperature. After 1.5 h at room temperature HgCl_2 (~75 mg, excess) was added in one portion. The heterogeneous reaction mixture was stirred for 45 min, diluted with ethyl acetate and filtered through a pad of celite. The filtrate was diluted with additional ethyl acetate and washed with dilute HCl , saturated sodium bicarbonate, brine and dried over MgSO_4 . Concentration in vacuo followed by flash chromatography of the residue on silica gel (10% methanol in ethyl acetate) gave 13 mg (16%) of the (mono methyl) bis-Boc guanidino ester 218 as a colorless foam.

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¹H NMR (CDCl_3 , 300 MHz): δ 86.84 (s, 1H); 6.20 (bd, 1H, J=5.1 Hz); 5.45 (bs, 1H); 4.25–4.40 (bm, 1H); 4.20–4.05 (bm, 2H); 3.76 (s, 3H); 3.60–3.50 (m, 1H); 3.43–3.30 (m, 1H); 2.90 (dd, 1H, J=5.4, 17.7 Hz); 2.77 (d, 3H, J=4.8 Hz); 2.35–2.25 (m, 1H); 1.96 (s, 3H); 1.60–1.50 (m, 2H); 1.47 (s, 9H); 0.91 (t, 3H, J=7.2 Hz).

Example 84

(mono methyl) bis-Boc guanidino acid 219: To a solution of methyl ester 218 (13 mg, 0.031 mmol) in THF (500 μ L) was added aqueous KOH (60 μ L of a 1.039N solution). The reaction mixture was stirred at room temperature for 1 h and then gently refluxed for 1 h. The reaction was cooled to 0° C. and acidified to pH 6.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration in vacuo gave the free acid 219 which was used without further purification in the next reaction.

Example 85

(mono methyl) guanidino amino acid 220: To a solution of (mono methyl) bis-Boc guanidyl acid 219 (crude from previous reaction) in CH_2Cl_2 (1.0 mL) cooled to 0° C. was added neat trifluoroacetic acid (1.0 mL). The reaction mixture was stirred at 0° C. for 1 h and then at room temperature for 1 h. Concentration in vacuo gave a pale solid which was purified by C_{18} reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 4.4 mg (33%, 2 steps) of the guanidine carboxylic acid 220.

¹H NMR (D_2O , 300 MHz): δ 86.52 (bs, 1H); 4.27 (bd, 1H, J=8.4 Hz); 4.01 (dd, 1H, J=9.2, 10.3 Hz); 3.86–3.75 (m, 1H); 3.75–3.67 (m, 1H); 3.60–3.49 (m, 1H); 2.85 (s, 3H); 2.80 (dd, 1H, J=5.1, 17.7 Hz); 2.47–2.37 (m, 1H); 2.04 (s, 3H); 1.64–1.50 (m, 2H); 0.90 (t, 3H, J=7.2 Hz).

Example 86

(R)-methyl propyl ester 221: $\text{BF}_3\text{Et}_2\text{O}$ (63 μ L, 0.51 mmol) was added to a solution of N-trityl aziridine 183 (150 mg, 0.341 mmol) in (R)-(–)-2-butanol (1.2 mL) under argon with stirring at room temperature. The pale solution was heated at 70° C. for 2 h and then concentrated in vacuo to give a brown residue which was dissolved in dry pyridine (2.0 mL) and treated with acetic anhydride (225 μ L) and a catalytic amount of DMAP (few crystals) at 0° C. The reaction was allowed to warm to room temperature and stirred for 2 h, concentrated in vacuo and partitioned between ethyl acetate and brine. The organic layer was separated and washed sequentially with dilute HCl , saturated sodium bicarbonate, brine and dried over MgSO_4 . Concentration in vacuo followed by flash chromatography of the residue on silica gel (50% hexanes in ethyl acetate) gave 75 mg (72%) of the (R)-methyl propyl ester 221 as a pale solid.

¹H NMR (CDCl_3 , 300 MHz): δ 86.79 (t, 1H, J=2.2 Hz); 6.14 (d, 1H, J=7.3 Hz); 4.55 (bd, 1H, J=8.7 Hz); 4.33–4.23 (m, 1H); 3.77 (s, 3H); 3.56–3.45 (m, 1H); 3.40–3.27 (m, 1H); 2.85 (dd, 1H, J=5.5, 17.5 Hz); 2.30–2.15 (m, 1H); 2.04 (s, 3H); 1.5901.40 (m, 2H); 1.10 (d, 3H, J=6.0 Hz); 0.91 (t, 3H, J=7.4 Hz).

Example 87

(R)-methyl propyl amino ester 222: Ph_3P (95 mg, 0.36 mmol) was added in one portion to a solution of azide 221 (75 mg, 0.24 mmol) and water (432 μ L) in THF (3.0 mL).

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The pale yellow solution was then heated at 50° C. for 10 h, cooled and concentrated in vacuo to give a pale solid. Purification by flash chromatography on silica gel (50% methanol in ethyl acetate) gave 66 mg (97%) of the amino ester 222 as a pale solid.

Example 88

Amino acid 223: A solution of methyl ester 222 (34 mg, 0.12 mmol) in THF (1.0 mL) was treated with aqueous KOH (175 μ L of a 1.039N solution). The reaction mixture was stirred at room temperature for 3 h and acidified to pH 6.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration in vacuo gave the amino acid as a pale solid which was purified by C_{18} reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 11.5 mg (36%) of the amino acid 223.

1 H NMR (D_2O , 300 MHz): δ 86.52 (bs, 1H); 4.28 (bd, 1H, J =8.7 Hz); 4.04 (dd, 1H, J =8.8, 11.5 Hz); 3.74–3.65 (m, 1H); 3.50–3.60 (m, 1H); 2.90 (dd, 1H, J =5.5, 17.2 Hz); 2.50–2.40 (m, 1H); 2.10 (s, 3H); 1.60–1.45 (m, 2H); 1.14 (d, 3H, J =6.2 Hz); 0.91 (t, 3H, J =7.4 Hz).

Example 89

bis-Boc guanidino ester 224: Treated according to the procedure of Kim and Qian, "Tetrahedron Lett.", 34:7677 (1993). To a solution of amine 222 (32 mg, 0.113 mmol), bis-Boc thiourea (32 mg, 0.115 mmol) and Et_3N (53 μ L) in dry DMF (350 μ L) cooled to 0° C. was added $HgCl_2$ (34 mg, 0.125 mmol) in one portion. The heterogeneous reaction mixture was stirred for 45 min at 0° C. and then at room temperature for 1 h, after which the reaction was diluted with $EtOAc$ and filtered through a pad of celite. Concentration in vacuo followed by flash chromatography of the residue on silica gel (20% hexanes in ethyl acetate) gave 57 mg (96%) of 224 as a colorless foam.

1 H NMR ($CDCl_3$, 300 MHz): δ 11.40 (s, 1H); 8.65 (d, 1H, J =7.8 Hz); 6.82 (s, 1H); 6.36 (d, 1H, J =8.7 Hz); 4.46–4.34 (m, 1H); 4.20–4.10 (m, 1H); 4.10–3.95 (m, 1H); 3.76 (s, 3H); 2.79 (dd, 1H, J =5.4, 17.7 Hz); 2.47–2.35 (m, 1H); 1.93 (s, 3H); 1.60–1.45 (m, 2H); 1.49 (s, 18H); 1.13 (d, 3H, J =6.0 Hz); 0.91 (t, 3H, J =7.5 Hz).

Example 90

Carboxylic acid 225: To a solution of methyl ester 224 (57 mg, 0.11 mmol) in THF (1.5 mL) was added aqueous KOH (212 μ L of a 1.039N solution). The reaction mixture was stirred at room temperature for 16 h, cooled to 0° C. and acidified to pH 4.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration in vacuo gave the free acid as a pale foam which was used without further purification in the next reaction.

Example 91

Guanidine carboxylic acid 226: To a solution of bis-Boc guanidinyl acid 225 (crude from previous reaction) in CH_2Cl_2 (4.0 mL) cooled to 0° C. was added neat trifluoroacetic acid (4.0 mL). The reaction mixture was stirred at 0° C. for 1 h and then at room temperature for 2 h. Concentration in vacuo gave a pale orange solid which was purified by C_{18} reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 18.4 mg (40%, 2 steps) of the guanidine carboxylic acid 226.

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1 H NMR (D_2O , 300 MHz): δ 86.47 (s, 1H); 4.28 (bd, 1H, J =8.4 Hz); 3.93–3.74 (m, 2H); 3.72–3.63 (m, 1H); 2.78 (dd, 1H, J =4.8, 17.4 Hz); 2.43–2.32 (m, 1H); 1.58–1.45 (m, 2H); 1.13 (d, 3H, J =6.0 Hz); 0.90 (t, 3H, J =7.4 Hz).

Example 92

(Diethyl) methyl ether ester 227: BF_3 . Et_2O (43 μ L, 0.35 mmol) was added to a solution of N-trityl aziridine 183 (104 mg, 0.24 mmol) in 3-pentanol (2.0 mL) under argon with stirring at room temperature. The pale solution was heated at 75° C. for 1.5 h and then concentrated in vacuo to give a brown residue which was dissolved in dry pyridine (2.0 mL) and treated with acetic anhydride (235 μ L) and a catalytic amount of DMAP (few crystals) at 0° C. The reaction was allowed to warm to room temperature and stirred for 1.5 h, concentrated in vacuo and partitioned between ethyl acetate and brine. The organic layer was separated and washed sequentially with dilute HCl, saturated sodium bicarbonate, brine and dried over $MgSO_4$. Concentration in vacuo followed by flash chromatography of the residue on silica gel (50% hexanes in ethyl acetate) gave 41 mg (53%) of the (Diethyl) methyl ether ester 227.

1 H NMR ($CDCl_3$, 300 MHz): δ 86.79 (t, 1H, J =2.1 Hz); 5.92 (d, 1H, J =7.5 Hz); 4.58 (bd, 1H, J =8.7 Hz); 4.35–4.25 (m, 1H); 3.77 (s, 3H); 3.36–3.25 (m, 2H); 2.85 (dd, 1H, J =5.7, 17.4 Hz); 2.29–2.18 (m, 1H); 2.04 (s, 3H); 1.60–1.45 (m, 4H); 0.91 (t, 3H, J =3.7 Hz); 0.90 (t, 3H, J =7.3 Hz).

Example 93

(Diethyl) methyl ether amino ester 228: Ph_3P (52 mg, 0.19 mmol) was added in one portion to a solution of azide 227 (41 mg, 0.13 mmol) and water (234 μ L) in THF (2.0 mL). The pale yellow solution was then heated at 50° C. for 10 h, cooled and concentrated in vacuo to give a pale solid. Purification by flash chromatography on silica gel (50% methanol in ethyl acetate) gave 31 mg (80%) of the amino ester 228 as a pale white solid.

1 H NMR ($CDCl_3$, 300 MHz): δ 86.78 (t, 1H, J =2.1 Hz); 5.68 (bd, 1H, J =7.8 Hz); 4.21–4.18 (m, 1H); 3.75 (s, 3H); 3.54–3.45 (m, 1H); 3.37–3.15 (m, 2H); 2.74 (dd, 1H, J =5.1, 17.7 Hz); 2.20–2.07 (m, 1H); 2.03 (s, 3H); 1.69 (bs, 2H, $—NH_2$); 1.57–1.44 (m, 4H); 0.90 (t, 3H, J =7.5 Hz); 0.89 (t, 3H, J =7.5 Hz).

Example 94

Amino acid 229: A solution of methyl ester 228 (31 mg, 0.104 mmol) in THF (1.0 mL) was treated with aqueous KOH (203 μ L of a 1.039N solution). The reaction mixture was stirred at room temperature for 2 h and acidified to pH 6.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration in vacuo gave the amino acid as a pale solid which was purified by C_{18} reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 14.3 mg (48%) of the amino acid 229.

1 H NMR (D_2O , 300 MHz): δ 86.50 (t, 1H, J =2.1 Hz); 4.30–4.26 (m, 1H); 4.03 (dd, 1H, J =9.0, 11.7 Hz); 3.58–3.48 (m, 2H); 2.88 (dd, 1H, J =5.4, 16.8 Hz); 2.53–2.41 (m, 1H); 1.62–1.40 (m, 4H); 0.90 (t, 3H, J =7.5 Hz); 0.85 (t, 3H, J =7.5 Hz).

Example 95

t-amyl ether ester 230: BF_3 . Et_2O (43 μ L, 0.35 mmol) was added to a solution of N-trityl aziridine 183 (104 mg, 0.24

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mmol) in t-amyl alcohol (2.5 mL) under argon with stirring at room temperature. The pale solution was heated at 75° C. for 3 h and then concentrated in vacuo to give a brown residue which was dissolved in dry pyridine (2.0 mL) and treated with acetic anhydride (250 μ L) and a catalytic amount of DMAP (few crystals). The reaction was stirred at room temperature for 1.5 h, concentrated in vacuo and partitioned between ethyl acetate and brine. The organic layer was separated and washed sequentially with dilute HCl, saturated sodium bicarbonate, brine and dried over MgSO₄. Concentration in vacuo followed by flash chromatography of the residue on silica gel (50% hexanes in ethyl acetate) gave 27 mg (35%) of the t-amyl ether ester 230 as a pale orange oil.

¹H NMR (CDCl₃, 300 MHz): 86.72 (t, 1H, J=2.1 Hz); 5.83 (d, 1H, J=7.2 Hz); 4.71 (bd, 1H, J=8.1 Hz); 4.45–4.35 (m, 1H); 3.75 (s, 3H); 3.27–3.17 (m, 1H); 2.84 (dd, 1H, J=5.7, 17.4 Hz); 2.27–2.15 (m, 1H); 2.05 (s, 3H); 1.57–1.47 (m, 2H); 1.19 (s, 3H); 1.15 (s, 3H); 0.90 (t, 3H, J=7.5 Hz).

Example 96

t-amyl ether amino ester 231: Ph₃P (35 mg, 0.133 mmol) was added in one portion to a solution of azide 230 (27 mg, 0.083 mmol) and water (160 μ L) in THF (1.5 mL). The pale orange solution was then heated at 50° C. for 10 h, cooled and concentrated in vacuo to give a pale solid. Purification by flash chromatography on silica gel (50% methanol in ethyl acetate) gave 20 mg (82%) of the amino ester 231 as a pale oil.

Example 97

Amino acid 232: A solution of methyl ester 231 (20 mg, 0.068 mmol) in THF (1.0 mL) was treated with aqueous KOH (131 μ L of a 1.039N solution). The reaction mixture was stirred at room temperature for 2.5 h and acidified to pH 5.0 with Amberlite IR-120 (H⁺) acidic resin. The resin was filtered and washed with water and methanol. Concentration in vacuo gave the amino acid as a pale solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 8.6 mg (45%) of the amino acid 232.

¹H NMR (D₂O, 300 MHz): 66.47 (bs, 1H); 4.42 (bd, 1H, J=8.1 Hz); 3.97 (dd, 1H, J=8.4, 11.4 Hz); 3.65–3.54 (m, 1H); 2.88 (dd, 1H, J=5.5, 17.3 Hz); 2.51–2.39 (m, 1H); 2.08 (s, 3H); 1.61–1.46 (m, 2H); 1.23 (s, 3H); 1.18 (s, 3H), 0.86 (t, 3H, J=7.5 Hz).

Example 98

n-Propyl thio ether ester 233: BF₃·Et₂O (130 μ L, 1.06 mmol) was added to a solution of N-trityl aziridine 183 (300 mg, 0.68 mmol) in 1-propanethiol (8.0 mL) under argon with stirring at room temperature. The pale solution was then heated at 65° C. for 45 min, concentrated and partitioned between ethyl acetate and brine. The organic layer was separated and washed with saturated sodium bicarbonate, brine and dried over MgSO₄. Concentration in vacuo followed by flash chromatography of the residue on silica gel (30% hexanes in ethyl acetate) gave 134 mg (73%) of the n-propyl thio ether ester 233 as a pale oil.

¹H NMR (CDCl₃, 300 MHz): 86.87 (t, 1H, J=2.4 Hz); 3.77 (s, 3H); 3.48–3.38 (m, 1H); 3.22–3.18 (m, 1H), 2.93 (dd, 1H, J=5.4, 17.4 Hz); 2.80 (t, 1H, J=9.9 Hz); 2.51 (t, 2H, J=7.2 Hz); 2.32–2.20 (m, 1H); 1.96 (bs, 2H, —NH₂), 1.69–1.56 (m, 2H); 1.00 (t, 3H, J=7.2 Hz).

Example 99

n-Propyl thio ether azido ester 234: To a solution of amine 233 (134 mg, 0.50 mmol) in pyridine (1.5 mL) cooled to 0°

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C. was added neat acetyl chloride (60 μ L, 0.84 mmol). After stirring for 1 h the reaction mixture was warmed to room temperature and stirred for an additional 15 min. The reaction was concentrated and partitioned between ethyl acetate and brine and washed sequentially with dilute HCl, water, saturated sodium bicarbonate, brine and dried over MgSO₄. Concentration in vacuo followed by flash chromatography of the residue on silica gel (30% hexanes in ethyl acetate) gave 162 mg (100%) of the n-Propyl thio ether 10 azido ester 234 as a pale yellow solid.

¹H NMR (CDCl₃, 300 MHz): 86.90 (t, 1H, J=2.7 Hz); 5.87 (bd, 1H, J=7.8 Hz); 4.07–3.98 (m, 1H); 3.77 (s, 3H); 3.65–3.55 (m, 1H); 2.95–2.85 (m, 1H); 2.60–2.45 (m, 2H); 2.30–2.18 (m, 1H); 2.08 (s, 3H); 1.65–1.53 (m, 2H); 0.98 (t, 3H, J=7.2 Hz).

Example 100

n-Propyl thio ether amino ester 235: The azide 234 (130 mg, 0.416 mmol) in ethyl acetate (10 mL) was hydrogenated (1 atmosphere) over Lindlar's catalyst (150 mg) for 18 h at room temperature. The catalyst was then filtered through a celite pad and washed with hot ethyl acetate and methanol. Concentration in vacuo followed by flash chromatography of the orange residue gave 62 mg (53%) of the n-propyl thio ether amino ester 235.

¹H NMR (CDCl₃, 300 MHz): 86.88 (t, 1H, J=2.7 Hz); 5.67 (bd, 1H, J=8.7 Hz); 3.76 (s, 3H); 3.75–3.65 (m, 1H); 3.45–3.35 (bm, 1H); 3.05–2.95 (m, 1H); 2.87–2.78 (m, 1H); 2.56–2.40 (m, 2H); 2.18–2.05 (m, 1H); 2.09 (s, 3H); 1.65–1.50 (m, 2H); 1.53 (bs, 2H, —NH₂); 0.98 (t, 3H, J=7.2 Hz).

Example 101

Compound 240: A suspension of Quinic acid (103 g), 2,2-dimethoxypropane (200 mL) and toluenesulfonic acid (850 mg) in acetone (700 mL) was stirred at room temperature for 4 days. Solvents and excess reagents were removed under reduced pressure. Purification by flash column chromatography (Hexanes/EtOAc=2/1–1.5/1) gave lactone 240 (84 g, 73%): ¹H NMR (CDCl₃) 84.72 (dd, J=2.4, 6.1 Hz, 1H), 4.50 (m, 1H), 4.31 (m, 1H), 2.67 (m, 2H), 2.4–2.2 (m, 3H), 1.52 (s, 3H), 1.33 (s, 3H).

Example 102

Compound 241: To a solution of lactone 240 (43.5 g, 203 mmol) in methanol (1200 mL) was added sodium methoxide (4.37M, 46.5 mL, 203 mmol) in one portion. The mixture was stirred at room temperature for 3 hrs, and quenched with acetic acid (11.62 mL). Methanol was removed under reduced pressure. The mixture was diluted with water, and extracted with EtOAc (3 \times). The combined organic phase was washed with water (1 \times) and brine (1 \times), and dried over MgSO₄. Purification by flash column chromatography (Hexanes/EtOAc=1/1 to 1/4) gave diol (43.4 g, 87%): ¹H NMR (CDCl₃) 84.48 (m, 1H), 4.13 (m, 1H), 3.99 (t, J=6.4 Hz, 1H), 3.82 (s, 3H), 3.34 (s, 1H), 2.26 (d, J=3.8 Hz, 2H), 2.08 (m, 1H), 1.91 (m, 1H), 1.54 (s, 3H), 1.38 (s, 3H).

Example 103

Compound 242: To a solution of diol 241 (29.8 g, 121 mmol) and 4-(N,N-dimethylamino)pyridine (500 mg) in pyridine (230 mL) was added tosyl chloride (27.7 g, 145 mmol). The mixture was stirred at room temperature for 3 days, and pyridine was removed under reduced pressure. The mixture was diluted with water, and extracted with

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EtOAc (3×). The combined organic phase was washed with water (2×) and brine (1×), and dried over MgSO₄. Concentration and purification by flash column chromatography (Hexanes/EtOAc=2/1-1/1) gave tosylate 242 (44.6 g, 92%): ¹H NMR (CDCl₃) δ7.84 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H), 4.76 (m, 1H), 4.42 (m, 1H), 4.05 (dd, J=5.5, 7.5 Hz, 1H), 3.80 (s, 3H), 2.44 (s, 3H), 2.35 (m, 1H), 2.24 (m, 2H), 1.96 (m, 1H), 1.26 (s, 3H), 1.13 (s, 3H).

Example 104

Compound 243: To a solution of tosylate 242 (44.6 g, 111.5 mmol) in CH₂Cl₂ (450 mL) at -78° C. was added pyridine (89 mL), followed by slow addition of SO₂Cl₂ (26.7 mL, 335 mmol). The mixture was stirred at -78° C. for 5 hrs, and methanol (45 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 12 hrs. Ethyl ether was added, and the mixture was washed with water (3×) and brine (1×), and dried over MgSO₄. Concentration gave the intermediate as a oil (44.8 g). To a solution of the intermediate (44.8 g, 111.5 mmol) in MeOH (500 mL) was added TsOH (1.06 g, 5.6 mmol). The mixture was refluxed for 4 hrs. The reaction mixture was cooled to room temperature, and methanol was removed under reduced pressure. Fresh methanol (500 mL) was added, and the whole mixture was refluxed for another 4 hrs. The reaction mixture was cooled to room temperature, and methanol was removed under reduced pressure. Purification by flash column chromatography (Hexanes/EtOAc=3/1-1/3) gave a mixture of the two isomers (26.8 g). Recrystallization from EtOAc/Hexanes afforded the pure desired product 243 (20.5 g, 54%): ¹H NMR (CDCl₃) δ7.82 (d, J=8.3 Hz, 2H), 7.37 (d, J=8.3 Hz, 2H), 6.84 (m, 1H), 4.82 (dd, J=5.8, 7.4 Hz, 1H), 4.50 (m, 1H), 3.90 (dd, J=4.4, 8.2 Hz, 1H), 3.74 (s, 3H), 2.79 (dd, J=5.5, 18.2 Hz, 1H), 2.42 (dd, J=6.6, 18.2 Hz, 1H).

Example 105

Compound 1: To a solution of diol 243 (20.0 g, 58.5 mmol) in THF (300 mL) at 0° C. was added DBU (8.75 mL, 58.5 mmol). The reaction mixture was warmed to room temperature, and stirred for 12 hrs. Solvent (THF) was removed under reduced pressure. Purification by flash column chromatography (Hexanes/EtOAc=1/3) gave epoxide 1 (9.72 g, 100%): ¹H NMR (CDCl₃) δ6.72 (m, 1H), 4.56 (td, J=2.6, 10.7 Hz, 1H), 3.76 (s, 3H), 3.56 (m, 2H), 3.0 (d, J=21 Hz, 1H), 2.50 (d, J=20 Hz, 1H), 2.11 (d, 10.9 Hz, 1H).

Example 106

Aziridine 244: A solution of allyl ether 4 (223 mg, 1.07 mmol) and Lindlar's catalyst (200 mg) in absolute ethanol (8.0 mL) was treated with hydrogen gas (1 atmosphere) at room temperature for 50 min. The catalyst was then filtered through a celite pad and washed with hot methanol. Concentration in vacuo gave ~230 mg of 244 as pale yellow oil which was used for the next reaction without any further purification.

Example 107

Azido amine 205: Crude aziridine 244 (230 mg), sodium azide (309 mg, 4.75 mmol) and ammonium chloride (105 mg, 1.96 mmol) in dry DMF (10 mL) was heated at 70° C. for 16 h under an argon atmosphere. The reaction was cooled, filtered through a fritted glass funnel to remove solids and partitioned between ethyl acetate and brine. The organic layer was separated and dried over MgSO₄. Concentration in vacuo followed by flash chromatography of the

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residue on silica gel (10% hexanes in ethyl acetate) gave 154 mg (57%, 2 steps) of 205 as a yellow viscous oil of sufficient purity for the next reaction.

Example 108

N-acetyl azide 245: Acetyl chloride (70 μ L, 0.98 mmol) was added to a solution of amine 205 (154 mg, 0.61 mmol) and pyridine (1.3 mL) in CH₂Cl₂ (4.0 mL) cooled to 0° C. After 1.5 h at 0° C. the reaction was concentrated and partitioned between ethyl acetate and brine. The organic layer was separated and washed sequentially with saturated sodium bicarbonate, brine and dried over MgSO₄. Concentration in vacuo followed by flash chromatography of the residue on silica gel (ethyl acetate) gave 167 mg (93%) of 245 as a pale yellow solid.

Example 109

Amino ester 200: Triphenyl phosphine (1.7 g, 6.48 mmol) was added in several portions to a solution of 245 (1.78 g, 6.01 mmol) in THF (40 mL) and water (1.5 mL). The reaction was then stirred at room temperature for 42.5 h. Volatiles were removed under vacuum and the crude solid absorbed onto silica gel and purified by flash chromatography on silica gel (100% ethyl acetate then 100% methanol) to give 1.24 g (77%) of 200 as a pale solid.

Example 110

Amino acid 102: To a solution of methyl ester 200 (368 mg, 1.37 mmol) in THF (4.0 mL) cooled to 0° C. was added aqueous NaOH (1.37 mL, of a 1.0N solution). The reaction mixture was stirred at 0° C. for 10 min, room temperature for 1.5 h and then acidified to pH 7.0-7.5 with Amberlite IR-120 (H⁺) acidic resin. The resin was filtered and washed with water and methanol. Concentration in vacuo gave the amino acid as a white solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 290 mg (83%) of amino acid 102.

Example 111

Amine hydrochloride 250: Amine 228 (15.6 mg, 0.05 mmol) was treated with 0.1N HCl and was evaporated. The residue was dissolved in water and was filtered through a small column of C-18 reverse phase silica gel. The hydrochloride salt 250 (12 mg) was obtained as a solid after lyophilization: ¹H NMR (D₂O) δ8.86 (s, 1H), 4.35 (br d, J=9.0), 4.06 (dd, 1H, J=9.0, 11.6), 3.79 (s, 3H), 3.65-3.52 (m, 2H), 2.97 (dd, 1H, J=5.5, 17.2), 2.58-2.47 (m, 1H), 2.08 (s, 3H), 1.61-1.41 (m, 4H), 0.88 (t, 3H, J=7.4), 0.84 (t, 3H, J=7.4).

Example 112

Bis-Boc-guanidine 251: To a solution of amine 228 (126 mg, 0.42 mmol), N,N'-bis-tert-butoxycarbonylthiourea (127 mg, 0.46 mmol), and triethylamine (123 μ L, 0.88 mmol) in DMF (4 mL) at 0° C. was added HgCl₂ (125 mg, 0.46 mmol). The mixture was stirred at 0° C. for 30 min and at room temperature for 1.5 h. The reaction was diluted with ethyl acetate and filtered through celite. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with saturated NaCl, dried (MgSO₄), filtered and the solvent was evaporated. The crude product was purified on silica gel (2/1, 1/1-hexane/ethyl acetate) to afford bis-Boc-guanidine 251 (155 mg, 69%) as a solid: ¹H NMR (CDCl₃) δ11.40 (s,

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1H), 8.66 (d, 1H, J=7.9), 6.8 (s, 1H), 6.22 (d, 1H, J=8.9), 4.43–4.34 (m, 1H), 4.19–4.08 (m, 1H), 4.03 (m, 1H), 3.76 (s, 3H), 3.35 (m, 1H), 2.79 (dd, 1H, J=5.4, 17.7), 2.47–2.36 (m, 1H), 1.92 (s, 3H), 1.50, 1.49 (2 s, 18H), 0.89 (m, 6H).

Example 113

Guanidino-acid 252: To a solution of bis-Boc-guanidine 251 (150 mg, 0.28 mmol) in THF (3 mL) was added 1.039N KOH solution (337 μ L) and water (674 μ L). The mixture was stirred for 3 h, additional 1.039N KOH solution (67 μ L) was added and stirring was continued for 2 h. The reaction was filtered to remove a small amount of dark precipitate. The filtrate was cooled to 0° C. and was acidified with IR 120 ion exchange resin to pH 4.5–5.0. The resin was filtered and washed with methanol. The filtrate was evaporated to a residue which was dissolved in CH_2Cl_2 (3 mL), cooled to 0° C., and was treated with trifluoroacetic acid (3 mL). After stirring 10 min. at 0° C., the reaction was stirred at room temperature for 2.5 h. The solvents were evaporated and the residue was dissolved in water and was chromatographed on a short column (3×1.5 cm) of C-18 reverse phase silica gel eluting initially with water and then 5% acetonitrile/water. Product fractions were combined and evaporated. The residue was dissolved in water and lyophilized to afford guanidino-acid 252 (97 mg, 79%) as a white solid.

Example 114

Azido acid 260: To a solution of methyl ester 227 (268 mg, 0.83 mmol) in THF (7.0 mL) was added aqueous KOH (1.60 mL of a 1.039N solution) at room temperature. After stirring for 19 h at room temperature the reaction was acidified to pH 4.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and ethanol. Concentration in vacuo gave the crude azido acid 260 as a pale orange foam which was used for the next reaction without any further purification.

Example 115

Azido ethyl ester 261: To a solution of carboxylic acid 260 (crude from previous reaction, assume 0.83 mmol), ethyl alcohol (150 μ L), and catalytic DMAP in CH_2Cl_2 (6.0 mL) was added DCC (172 mg, 0.83 mmol) in one portion at room temperature. After several minutes a precipitate formed and after an additional 1 h of stirring the reaction was filtered and washed with CH_2Cl_2 . Concentration in vacuo afforded a pale solid which was purified by flash chromatography on silica gel (50% hexanes in ethyl acetate) to give 272 mg (96%, small amount of DCU impurity present) of 261 as a white solid.

Example 116

Amino ethyl ester 262: Triphenyl phosphine (342 mg, 1.30 mmol) was added in one portion to a solution of 261 (272 g, 0.80 mmol) in THF (17 mL) and water (1.6 mL). The reaction was then heated at 50° C. for 10 h, cooled and concentrated in vacuo to give a pale white solid. Purification of the crude solid by flash chromatography on silica gel (50% methanol in ethyl acetate) gave 242 mg (96%) of the amino ethyl ester 262 as a pale solid. The amino ethyl ester is dissolved in 3N HCl and lyophilized to give the corresponding water soluble HCl salt form.

¹H NMR (D_2O , 300 MHz): 86.84 (s, 1H); 4.36–4.30 (br m, 1H); 4.24 (q, 2H, J=7.2 Hz); 4.05 (dd, 1H, J=9.0, 11.7 Hz); 3.63–3.50 (m, 2H); 2.95 (dd, 1H, J=5.7, 17.1 Hz); 2.57–2.45 (m, 1H); 1.60–1.39 (m, 4H); 1.27 (t, 3H, J=7.2 Hz); 0.89–0.80 (m, 6H).

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Example 117

bis-Boc guanidino ethyl ester 263: Treated according to the procedure of Kim and Qian, "Tetrahedron Lett." 34:7677 (1993). To a solution of amine 262 (72 mg, 0.23 mmol), bis-Boc thiourea (66 mg, 0.24 mmol) and Et_3N (108 μ L) in dry DMF (600 μ L) cooled to 0° C. was added HgCl_2 (69 mg, 0.25 mmol) in one portion. The heterogeneous reaction mixture was stirred for 1 h at 0° C. and then at room temperature for 15 min, after which the reaction was diluted with EtOAc and filtered through a pad of celite. Concentration in vacuo followed by flash chromatography of the residue on silica gel (20% hexanes in ethyl acetate) gave 113 mg (89%) of 263 as a colorless foam.

¹H NMR (CDCl_3 , 300 MHz): δ 11.41 (s, 1H); 8.65 (d, 1H, J=8.1 Hz); 6.83 (s, 1H); 6.22 (d, 1H, J=9.0 Hz); 4.46–4.34 (m, 1H); 4.21 (q, 2H, J=6.9 Hz); 4.22–4.10 (m, 1H); 4.04–4.00 (m, 1H); 3.36 (quintet, 1H, J=5.7 Hz); 2.78 (dd, 1H, J=5.4, 17.7 Hz); 2.46–2.35 (m, 1H); 1.94 (s, 3H); 1.60–1.40 (m, 4H); 1.49 (s, 9H); 1.50 (s, 9H); 1.30 (t, 3H, J=6.9 Hz); 0.93–0.84 (m, 6H).

Example 118

Guanidino ethyl ester 264: To a solution of bis-Boc guanidinyl ethyl ester 263 (113 mg, 0.20 mmol) in CH_2Cl_2 (5.0 mL) cooled to 0° C. was added neat trifluoroacetic acid (5.0 mL). The reaction mixture was stirred at 0° C. for 30 min and then at room temperature for 1.5 h. The reaction was then concentrated in vacuo to give a pale orange solid which was purified by C_{18} reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 63 mg (66%) of the guanidine ethyl ester 264 as white solid.

¹H NMR (D_2O , 300 MHz): δ 6.82 (s, 1H); 4.35–4.31 (m, 1H); 4.24 (q, 2H, J=7.1 Hz); 3.95–3.87 (m, 1H); 3.85–3.76 (m, 1H); 3.57–3.49 (m, 1H); 2.87 (dd, 1H, J=5.1, 17.7 Hz); 2.46–2.34 (m, 1H); 2.20 (s, 3H); 1.60–1.38 (m, 4H); 1.28 (t, 3H, J=7.1 Hz); 0.90–0.80 (m, 6H).

Example 119

Enzyme Inhibition: Using the methods of screening in vitro activity described above, the following activities were observed (+10–100 μ M, ++1–10 μ M, +++<1.0 μ M):

	Compound	IC_{50}
45	102/103(2:1)	++
	8	++
	A.17.aA.i	++
	114	++
	A.1.a.4.i	++
	79	+
50	82/75 (1.2:1)	+
	94	+++
	A.100.a.11.i	+++
	A.101.a.11.i	+++
55	A.113.a.4.i	+++

Example 120

Compounds A.113.b.4.i and A.113.x.4.i were incubated separately in enzyme assay buffy and tested for activity as described in Example 119. Activity was >100 μ M for both. When each compound was separately incubated in rat plasma prior to testing as described in Example 119, activity of both was similar to compound A.113.a.4.i.

Example 121

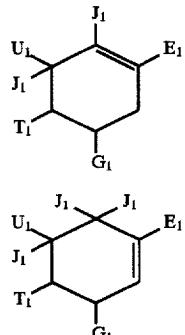
Compound A.4.a.11.i was tested in BAIB/c mice. An intraperitoneal dose of 10–50 mg/kg/day and an oral dose of

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100 mg/kg/day were effective to protect the mice against Influenza A virus.

Further numbered embodiments follow:

1. A composition comprising a compound of formula (I) or (II):



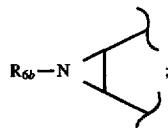
wherein

E₁ is $-(CR_1R_1)_{m_1}W_1$;

G₁ is N₃, —CN, —OH, —OR_{6a}, —NO₂, or $-(CR_1R_1)$

T₁ is $^{m_1}W_2$;

T₁ is NR_1W_3 , a heterocycle, or is taken together with U₁ or G₁ to form a group having the structure



U₁ is H or $-X_1W_6$;

J₁ is independently H, F or Cl;

R₁ is independently H or alkyl of 1 to 12 carbon atoms;

R₂ is independently R₃ or R₄ wherein each R₄ is independently substituted with 0 to 3 R₃ groups;

R₃ is independently F, Cl, Br, I, —CN, N₃, —NO₂,

—OR_{6a}, —OR₁, —N(R₁)₂, —N(R₁)(R_{6b}),

—N(R_{6b})₂, —SR₁, —SR_{6a}, —SOR₁, —S(O)₂R₁,

—S(O)R_{6a}, —S(O)₂R_{6a}, —C(O)OR₁, —C(O)R_{6c},

—C(O)OR_{6a}, —OC(O)R₁, —NR₁C(O)R₁,

—N(R_{6b})C(O)R₁, —C(O)N(R₁)₂, —C(O)N(R_{6b})

(R₁), —C(O)N(R_{6b})₂, —C(NR₁)(N(R₁))₂, —C(N

(R_{6b}))(N(R_{6b}))₂, —N(R₁)C(N(R₁))(N(R₁))₂,

—N(R₁)(N(R_{6b}))(N(R₁)), —N(R₁)C(N(R_{6b}))

(N(R₁))(N(R_{6b})), —N(R_{6b})C(N(R₁))(N(R₁)), —N(R₁)

C(N(R_{6b}))(N(R₁)), —N(R_{6b})C(N(R_{6b}))(N(R₁)),

—N(R_{6b})C(N(R₁))(N(R_{6b})), —N(R_{6b})C(N(R₁))

(N(R₁))(N(R_{6b})), —N(R_{6b})C(N(R_{6b}))(N(R_{6b}))(N(R_{6b})),

—N(R₁)C(N(R₁))(N(R_{6b}))₂, —N(R_{6b})C(N(R₁))(N

(R_{6b}))₂, —N(R₁)C(N(R_{6b}))(N(R_{6b}))₂, =O, =S,

=N(R_{6b}) or =N(R₁);

R₄ is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R₅ is independently R₄ wherein each R₄ is substituted with 0 to 3 R₃ groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R₃ groups;

R_{6a} is independently H or a protecting group for hydroxyl or thio;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

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R_{6c} is independently H or the residue of an amino-containing compound;

W₁ is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

W₂ is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W₃ is W₄ or W₅;

W₄ is R₅ or $—C(O)R_5$, $—C(O)W_5$, $—SO_2R_5$, or $—SO_2W_5$;

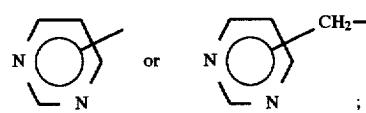
W₅ is carbocycle or heterocycle wherein W₅ is independently substituted with 0 to 3 R₂ groups;

W₆ is R₅, —W₅, $—R_{5a}W_5$, $—C(O)\bar{O}R_{6b}$, $—C(O)R_{6c}$, $—C(O)NR_{6b}R_{6b}$, $—C(NR_{6b})NR_{6b}R_{6b}$, $—C(S)NR_{6b}R_{6b}$, or $—C(O)R_2$;

X₁ is a bond, $—O—$, $—NR_5—$, $—N(OR_5)—$, $—N(NR_5R_5)—$, $—S—$, $—SO—$, or $—SO_2—$; and each m₁ is independently an integer from 0 to 2; provided, however, that compounds are excluded wherein:

(a) E₁ is $—CO_2H$, $—P(O)(OH)_2$, $—NO_2$, $—SO_2H$, $—SO_3H$, tetrazolyl, $—CH_2CHO$, $—CHO$, or $—CH(CHO)_2$;

(b) G₁ is $—CN$, NR₂₀, N₃, $—O(R_{20})$, SR₂₀, guanidino, $—N(R_{20})(OR_{20})$, $—N(R_{20})\rightarrow O$, NHR₂₀, $—N(H)(R_{20})N(R_{20})_2$.



(c) T₁ is $—NHR_{20}$ or $—NO_2$;

(d) R₂₀ is H; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; an allyl group or an unsubstituted aryl group or an aryl substituted by a halogen, an OH group, an NO₂ group, an NH₂ group or a COOH group;

(e) J₁ is H;

(f) U₁ is $—CH_2YR_{20a}$, $—CH(YR_{20a})CH_2YR_{20a}$ or $—CH(YR_{20a})CH(YR_{20a})CH_2YR_{20a}$;

(g) R_{20a} is H or acyl having 1 to 4 carbon atoms;

(h) Y is O or S;

(i) 0 to 2 YR_{20a} are H, and

(j) successive Y moieties in a U₁ group are the same or different, and

the pharmaceutically acceptable salts thereof; and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

2. The composition of Embodiment 1 where further excluded are compounds wherein G₁ is $—N(R_{21})C(=N(R_{21}))N(R_{21})_2$ and R₂₁ is independently H, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkoxy, aryl, aralkyl, aryloxy, aralkyloxy, amino, hydroxy, cyano, nitro, COR₂₂, CO₂R₂₂, SO₂R₂₂ (where R₂₂ is C₁-C₆ alkyl or aralkyl), or CONR₂₃ (where R₂₃ is independently H or C₁-C₆ alkyl or aralkyl).

3. The composition of Embodiment 1 wherein X₁ is a bond and W₆ is $—R_5$, $—W_5$ or $—R_{5a}W_5$.

4. The composition of Embodiment 1 wherein X₁ is a bond and W₆ is R₅.

5. The composition of Embodiment 4 wherein R₅ is R₄ substituted with 0 to 3 $—OR_1$.

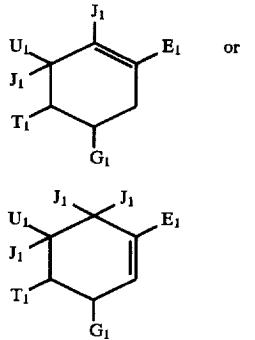
6. The composition of Embodiment 4 wherein R₅ is R₄ substituted with 0 to 3 $—NO_2$ or N₃ groups.

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7. The composition of Embodiment 5 wherein $-\text{OR}_1$ is present and at least one R_1 is $\text{C}_4\text{-C}_{12}$;

8. The composition of Embodiment 5 wherein R_4 is branched alkyl;

9. A composition comprising a compound of formula (I) or (II):



(I)

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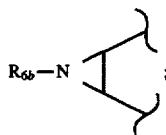
(II)

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wherein

E_1 is $-(\text{CR}_1\text{R}_1)_{m_1}\text{W}_1$;
 G_1 is N_3 , $-\text{CN}$, $-\text{OH}$, $-\text{OR}_{6a}$, $-\text{NO}_2$, or $-(\text{CR}_1\text{R}_1)_{m_1}\text{W}_2$;
 T_1 is $-\text{NR}_1\text{W}_3$, a heterocycle, or is taken together with U_1 or G_1 to form a group having the structure



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 U_1 is H or $-\text{X}_1\text{W}_6$; J_1 is independently H, F or Cl; R_1 is independently H or alkyl of 1 to 12 carbon atoms; R_2 is independently R_3 or R_4 wherein each R_4 is independently substituted with 0 to 3 R_3 groups;

R_3 is independently F, Cl, Br, I, $-\text{CN}$, N_3 , $-\text{NO}_2$, $-\text{OR}_{6a}$, $-\text{OR}_1$, $-\text{N}(\text{R}_1)_2$, $-\text{N}(\text{R}_1)(\text{R}_{6b})$, $-\text{N}(\text{R}_{6b})_2$, $-\text{SR}_1$, $-\text{SR}_{6a}$, $-\text{SOR}_1$, $-\text{S}(\text{O})_2\text{R}_1$, $-\text{S}(\text{O})\text{R}_{6a}$, $-\text{S}(\text{O})_2\text{R}_{6a}$, $-\text{C}(\text{O})\text{OR}_1$, $-\text{C}(\text{O})\text{R}_{6a}$, $-\text{C}(\text{O})\text{OR}_{6a}$, $-\text{OC}(\text{O})\text{R}_1$, $-\text{NR}_1\text{C}(\text{O})\text{R}_1$, $-\text{N}(\text{R}_{6b})\text{C}(\text{O})\text{R}_1$, $-\text{C}(\text{O})\text{N}(\text{R}_{6b})$, $(\text{R}_1)_2\text{C}(\text{O})\text{N}(\text{R}_{6b})_2$, $-\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_{6b}))$, $-\text{C}(\text{N}(\text{R}_{6b}))(\text{N}(\text{R}_{6b}))_2$, $-\text{N}(\text{R}_1)\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_{6b}))$, $-\text{N}(\text{R}_1)\text{C}(\text{N}(\text{R}_{6b}))$, $(\text{N}(\text{R}_1)(\text{R}_{6b}))_2$, $-\text{N}(\text{R}_{6b})\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_{6b}))_2$, $-\text{N}(\text{R}_1)\text{C}(\text{N}(\text{R}_{6b}))(\text{N}(\text{R}_1)_2)$, $-\text{N}(\text{R}_{6b})\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_1)_2)$, $-\text{N}(\text{R}_{6b})\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_1))_2$, $-\text{N}(\text{R}_{6b})\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_{6b}))_2$, $-\text{N}(\text{R}_1)\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_{6b}))_2$, $-\text{N}(\text{R}_{6b})\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_{6b}))_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}_{6b})$ or $=\text{N}(\text{R}_1)$;

R_4 is independently alkyl of 1 to 12 carbon atoms, 55 alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

 R_5 is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, 60 alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms which is substituted with 0-3 R_3 groups;

 R_{6a} is independently H or a protecting group for hydroxyl or thio; R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

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R_{6c} is independently H or the residue of an amino-containing compound;

W_1 is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

W_2 is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

 W_3 is W_4 or W_5 ;

W_4 is R_5 or $-\text{C}(\text{O})\text{R}_5$, $-\text{C}(\text{O})\text{W}_5$, $-\text{SO}_2\text{R}_5$, or $-\text{SO}_2\text{W}_5$;

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

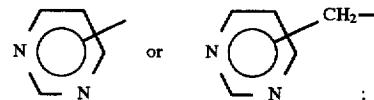
W_6 is $-\text{R}_5$, $-\text{W}_5$, $-\text{R}_{5a}\text{W}_5$, $-\text{C}(\text{O})\text{OR}_{6a}$, $-\text{C}(\text{O})\text{R}_{6c}$, $-\text{C}(\text{O})\text{NR}_{6b}\text{R}_{6b}$, $-\text{C}(\text{N}\text{R}_{6b})\text{NR}_{6b}\text{R}_{6b}$, $-\text{C}(\text{S})\text{NR}_{6b}\text{R}_{6b}$, or $-\text{C}(\text{O})\text{R}_2$;

X_1 is a bond, $-\text{O}-$, $-\text{NR}_5-$, $-\text{N}(\text{OR}_5)-$, $-\text{N}(\text{NR}_5\text{R}_5)-$, $-\text{S}-$, $-\text{SO}-$, or $-\text{SO}_2-$;

and each m_1 is independently an integer from 0 to 2; provided, however, that compounds are excluded wherein:

(a) E_1 is $-\text{CO}_2\text{H}$, $-\text{P}(\text{O})(\text{OH})_2$, $-\text{NO}_2$, $-\text{SO}_2\text{H}$, $-\text{SO}_3\text{H}$, tetrazolyl, $-\text{CH}_2\text{CHO}$, $-\text{CHO}$, or $-\text{CH}(\text{CHO})_2$;

(b) G_1 is $-\text{CN}$, NR_{20} , N_3 , $-\text{O}(\text{R}_{20})$, SR_{20} , guanidino, $-\text{N}(\text{R}_{20})(\text{OR}_{20})$, $-\text{N}(\text{R}_{20})-\text{O}-$, NHR_{20} , $-\text{N}(\text{H})(\text{R}_{20})\text{N}(\text{R}_{20})_2$,



(c) T_1 is $-\text{NHR}_{20}$ or $-\text{NO}_2$;

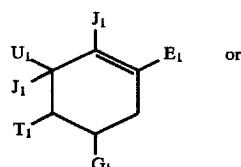
(d) R_{20} is H; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; an allyl group or an unsubstituted aryl group or an aryl substituted by a halogen, an OH group, an NO_2 group, an NH_2 group or a COOH group;

(e) J_1 is H;

(f) U_1 is $-\text{CH}_2\text{YR}_{20}$, $-\text{CHYR}_{20}\text{CH}_2\text{YR}_{20}$ or $-\text{CHYR}_{20}\text{CHYR}_{20}\text{CH}_2\text{YR}_{20}$;

(g) Y is O, S, H or NH, successive Y moieties in a U_1 group are the same or different, and when Y is H then R_{20} is a covalent bond, and the pharmaceutically acceptable salts and derivatives thereof; and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

10. A composition comprising a compound of formula (I) or (II):

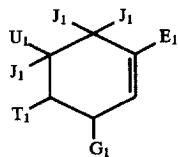


(I)

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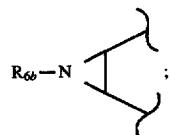


(II)

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wherein

E_1 is $-(CR_1R_1)_{m_1}W_1$;
 G_1 is N_3 , $-CN$, $-OH$, $-OR_{6a}$, $-NO_2$, or 10
 $-(CR_1R_1)_{m_1}W_2$;
 T_1 is $-NR_1W_3$, a heterocycle, or is taken together with
 U_1 or G_1 to form a group having the structure



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 U_1 is H or $-X_1W_6$; J_1 is independently H , F or Cl ; R_1 is independently H or alkyl of 1 to 12 carbon atoms;
 R_2 is independently R_3 or R_4 wherein each R_4 is
independently substituted with 0 to 3 R_3 groups;

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R_3 is independently F , Cl , Br , I , $-CN$, N_3 , $-NO_2$,
 $-OR_{6a}$, $-OR_1$, $-N(R_1)_2$, $-N(R_1)(R_{6b})$,
 $-N(R_{6b})_2$, $-SR_1$, $-SR_{6a}$, $-SOR_1$, $-S(O)R_1$,
 $-S(O)R_{6a}$, $-S(O)_2R_{6a}$, $-C(O)OR_1$, $-C(O)R_{6c}$,
 $-C(O)OR_{6a}$, $-OC(O)R_1$, $-NR_1C(O)R_1$,
 $-N(R_{6b})C(O)R_1$, $-C(O)N(R_1)_2$, $-C(O)N(R_{6b})$
 (R_1) , $-C(O)N(R_{6b})_2$, $-C(NR_1)(N(R_1)_2)$, $-C(N$
 $(R_{6b}))N(R_{6b})_2$, $-N(R_1)C(N(R_1))(N(R_1)_2)$,
 $-N(R_1)C(N(R_1))(N(R_{6b}))$, $-N(R_1)C(N(R_{6b}))$
 $(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1))(N(R_1)_2)$, $-N(R_1)$
 30
 $C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)_2)$,
 $-N(R_{6b})C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1))$
 $(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_{6b}))(N(R_{6b})(R_{6b}))$,
 $-N(R_1)C(N(R_1))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_1))(N$
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 $(R_{6b})_2)$, $-N(R_1)C(N(R_{6b}))(N(R_{6b})_2)$, $=O$, $=S$, $=N(R_{6b})$ or $=N(R_1)$;

 R_4 is independently alkyl of 1 to 12 carbon atoms,
alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to
12 carbon atoms; R_5 is independently R_4 wherein each R_4 is substituted
with 0 to 3 R_3 groups; R_{5a} is independently alkylene of 1 to 12 carbon atoms,
alkenylene of 2 to 12 carbon atoms, or alkynylene of
2-12 carbon atoms which is substituted with 0-3 R_3
groups;

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 R_{6a} is independently H or a protecting group for
hydroxyl or thio; R_{6b} is independently H , a protecting group for amino or
the residue of a carboxyl-containing compound; R_{6c} is independently H or the residue of an amino-
containing compound; W_1 is a group comprising an acidic hydrogen, a
protected acidic group, or an R_{6c} amide of the group
comprising an acidic hydrogen; W_2 is a group comprising a basic heteroatom or a
protected basic heteroatom, or an R_{6b} amide of the
basic heteroatom; W_3 is W_4 or W_5 ; W_4 is R_5 or $-C(O)R_5$, $-C(O)W_5$, $-SO_2R_5$, or
 $-SO_2W_5$;

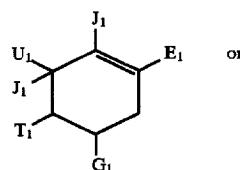
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 W_5 is a heterocycle wherein W_5 is independently
substituted with 0 to 3 R_2 groups;

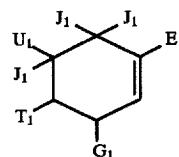
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W_6 is branched chain C_3-C_{12} alkyl substituted with 0
to 3 R_3 other than $-OPRT$ wherein PRT is a
protecting group;
 X_1 is a bond, $-O-$, $-NR_5-$, $-N(OR_5)-$,
 $-N(NR_5R_5)-$, $-S-$, $-SO-$, or $-SO_2-$; and
each m_1 is independently an integer from 0 to 2;
and the salts, solvates, resolved enantiomers and purified
diastereomers thereof.

11. The composition of Embodiment 10 wherein PRT is aralkyl, acyl, silyl ether, tetrahydropyranyl, 3-bromotetrahydropyranyl or tetrahydrothiopyranyl.
12. A composition comprising a compound of formula (I) or (II):



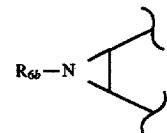
(I)



(II)

wherein

E_1 is $-(CR_1R_1)_{m_1}W_1$;
 G_1 is N_3 , $-CN$, $-OH$, $-OR_{6a}$, $-NO_2$, or
 $-(CR_1R_1)_{m_1}W_2$;
 T_1 is $-NR_1W_3$, a heterocycle, or is taken together with
 U_1 or G_1 to form a group having the structure

 U_1 is H or $-X_1W_6$; J_1 is independently H , F or Cl ; R_1 is independently H or alkyl of 1 to 12 carbon atoms;
 R_2 is independently R_3 or R_4 wherein each R_4 is
independently substituted with 0 to 3 R_3 groups;

R_3 is independently F , Cl , Br , I , $-CN$, N_3 , $-NO_2$,
 $-OR_{6a}$, $-OR_1$, $-N(R_1)_2$, $-N(R_1)(R_{6b})$,
 $-N(R_{6b})_2$, $-SR_1$, $-SR_{6a}$, $-SOR_1$, $-S(O)R_1$,
 $-S(O)R_{6a}$, $-S(O)_2R_{6a}$, $-C(O)OR_1$, $-C(O)R_{6c}$,
 $-C(O)OR_{6a}$, $-OC(O)R_1$, $-NR_1C(O)R_1$,
 $-N(R_{6b})C(O)R_1$, $-C(O)N(R_1)_2$, $-C(O)N(R_{6b})$
 (R_1) , $-C(O)N(R_{6b})_2$, $-C(NR_1)(N(R_1)_2)$, $-C(N$
 $(R_{6b}))N(R_{6b})_2$, $-N(R_1)C(N(R_1))(N(R_1)_2)$,
 $-N(R_1)C(N(R_1))(N(R_{6b}))$, $-N(R_1)C(N(R_{6b}))$
 $(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1))(N(R_1)_2)$, $-N(R_1)$
 $C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)_2)$,
 $-N(R_{6b})C(N(R_1))(N(R_{6b}))$, $-N(R_{6b})C(N(R_1))$
 $(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_{6b}))(N(R_{6b})(R_{6b}))$,
 $-N(R_1)C(N(R_1))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_1))(N$
 40
 $(R_{6b})_2)$, $-N(R_1)C(N(R_{6b}))(N(R_{6b})_2)$, $=O$, $=S$, $=N(R_{6b})$ or $=N(R_1)$;

 R_4 is independently alkyl of 1 to 12 carbon atoms,
alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to
12 carbon atoms; R_5 is independently R_4 wherein each R_4 is substituted
with 0 to 3 R_3 groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms which is substituted with 0-3 R_3 groups;

R_{6a} is independently H or a protecting group for hydroxyl or thio; 5

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

W_1 is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen; 10

W_2 is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom; 15

W_3 is W_4 or W_5 ;

W_4 is R_5 or $—C(O)R_5$, $—C(O)W_5$, $—SO_2R_5$, or $—SO_2W_5$;

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups; 20

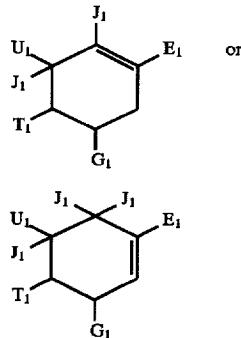
W_6 is $—(CH_2)_{m_1}CH((CH_2)_{m_3}R_3)_2$, $—(CH_2)_{m_1}C((CH_2)_{m_3}R_3)_3$; $—(CH_2)_{m_1}CH((CH_2)_{m_3}R_{5a}W_5)_2$; $—(CH_2)_{m_1}CH((CH_2)_{m_3}R_3)((CH_2)_{m_3}R_{5a}W_5)$; $—(CH_2)_{m_1}C((CH_2)_{m_3}R_3)_2(CH_2)_{m_3}R_{5a}W_5$, $(CH_2)_{m_1}C((CH_2)_{m_3}R_{5a}W_5)_3$ or $—(CH_2)_{m_1}C((CH_2)_{m_3}R_3)(CH_2)_{m_3}R_{5a}W_5)_2$; 25

m_3 is an integer from 1 to 3;

X_1 is a bond, $—O—$, $—NR_4—$, $—N(OR_4)—$, $—N(NR_4R_4)—$, $—S—$, $—SO—$, or $—SO_2—$; and each m_1 is independently an integer from 0 to 2; 30

and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

13. A composition comprising a compound of formula (I) or (III):

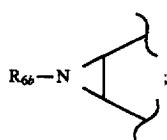


wherein

E_1 is $—(CR_1R_1)_{m_1}W_1$; 50

G_1 is N_3 , $—CN$, $—OH$, $—OR_{6a}$, $—NO_2$, or $—(CR_1R_1)_{m_1}W_2$;

T_1 is $—NR_1W_3$, a heterocycle, or is taken together with U_1 or G_1 to form a group having the structure 55



U_1 is H or $—X_1W_6$;

J_1 is independently H, F or Cl;

R_1 is independently H or alkyl of 1 to 12 carbon atoms; 65

R_2 is independently R_3 or R_4 wherein each R_4 is independently substituted with 0 to 3 R_3 groups;

R_3 is independently F, Cl, Br, I, $—CN$, N_3 , $—NO_2$, $—OR_{6a}$, $—OR_1$, $—N(R_1)(R_{6b})$, $—(R_{6b})_2$, $—SR_1$, $—SR_{6a}$, $—SOR_1$, $—S(O)_2R_1$, $—S(O)R_{6a}$, $—S(O)_2R_{6a}$, $—C(O)OR_1$, $—C(O)R_{6c}$, $—C(O)OR_{6a}$, $—OC(O)R_1$, $—NR_1C(O)R_1$, $—N(R_{6b})C(O)R_1$, $—C(O)N(R_1)_2$, $—C(O)N(R_{6b})(R_1)$, $—C(O)N(R_{6b})_2$, $—C(NR_1)(N(R_1)_2)$, $—C(N(R_{6b}))(N(R_{6b})_2)$, $—N(R_1)C(N(R_1))(N(R_1)_2)$, $—N(R_1)C(N(R_1))(N(R_1)(R_{6b}))$, $—N(R_1)C(N(R_1))(N(R_{6b}))$, $—N(R_1)C(N(R_{6b}))(N(R_1)_2)$, $—N(R_{6b})C(N(R_1))(N(R_1)(R_{6b}))$, $—N(R_{6b})C(N(R_1))(N(R_{6b})_2)$, $—N(R_{6b})C(N(R_1))(N(R_{6b}))$, $—N(R_{6b})C(N(R_{6b}))(N(R_{6b})_2)$, $=O$, $=S$, $=NR_{6b}$ or $=N(R_1)$;

R_4 is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R_5 is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms which is substituted with 0-3 R_3 groups;

R_{6a} is independently H or a protecting group for hydroxyl or thio;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

W_1 is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

W_2 is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W_3 is W_4 or W_5 ;

W_4 is R_5 or $—C(O)R_5$, $—C(O)W_5$, $—SO_2R_5$, or $—SO_2W_5$;

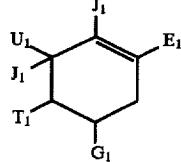
W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

W_6 is $—(CH_2)_{m_1}CH((CH_2)_{m_3}R_3)_2$, $—(CH_2)_{m_1}C((CH_2)_{m_3}R_3)_3$, $—(CH_2)_{m_1}CH((CH_2)_{m_3}R_{5a}W_5)_2$, $—(CH_2)_{m_1}CH((CH_2)_{m_3}R_3)((CH_2)_{m_3}R_{5a}W_5)$; $—(CH_2)_{m_1}C((CH_2)_{m_3}R_3)_2(CH_2)_{m_3}R_{5a}W_5$, $(CH_2)_{m_1}C((CH_2)_{m_3}R_{5a}W_5)_3$ or $—(CH_2)_{m_1}C((CH_2)_{m_3}R_3)((CH_2)_{m_3}R_{5a}W_5)_2$;

X_1 is $—O—$, $—NR_4—$, $—N(OR_4)—$, $—N(NR_4R_4)—$, $—S—$, $—SO—$, or $—SO_2—$;

and each m_1 is independently an integer from 0 to 2; and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

14. A composition comprising a compound of formula (I):



wherein

E_1 is $—(CR_1R_1)_{m_1}W_1$;

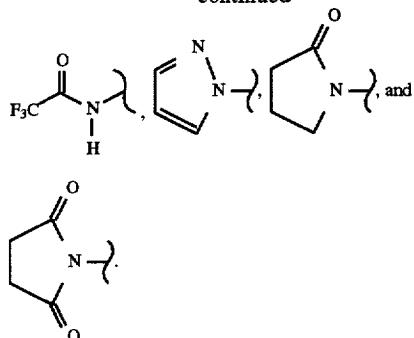
G_1 is N_3 , $—CN$, $—OH$, $—OR_{6a}$, $—NO_2$, or $—(CR_1R_1)_{m_1}W_2$;

T_1 is $—NR_1W_3$, a heterocycle, or is taken together with U_1 or G_1 to form a group having the structure

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-continued



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26. The composition of Embodiment 1 wherein X_1 is $-\text{O}-$ or $-\text{NR}_1-$

27. The composition of Embodiment 1 wherein W_6 is secondary or tertiary alkyl containing 3 to 12 carbon atoms which is unsubstituted or substituted with nitro, azido or halo.

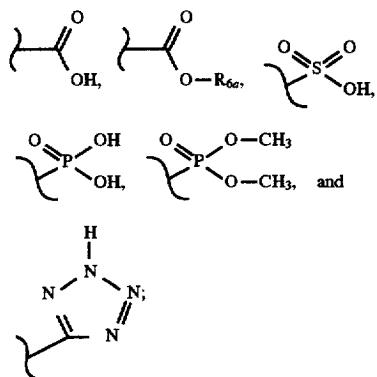
28. The composition of Embodiment 1 wherein W_6 is $-(\text{CH}_2)_{m_1} \text{CH}(\text{R}_1)_a \text{W}_7$, wherein W_7 is an alkyl of 1 to 4 carbon atoms substituted with 0 to 3 R_3 , a is 0 or 1, and when a is 0 then W_7 is joined to CH by a double bond.

29. The composition of Embodiment 28 wherein U_1 is $-\text{O}-\text{CH}_2\text{CH}(\text{R}_1)\text{W}_7$.

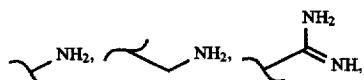
30. The composition of Embodiment 29 wherein W_7 is $-\text{CH}_2\text{OR}_1$ and R_1 is C_4-C_{12} alkyl.

31. The composition of Embodiment 1 wherein U_1 is selected from the group consisting of $\text{CH}_3(\text{CH}_2)_4\text{O}-$, $\text{CH}_3(\text{CH}_2)_3\text{O}-$, $\text{CH}_3(\text{CH}_2)_2\text{O}-$, $(\text{CH}_3\text{CH}_2)_2\text{CHO}-$, $(\text{CH}_3\text{CH}_2)(\text{CH}_3)\text{CHO}-$, $(\text{CH}_3)_2\text{CHO}-$, $(\text{CH}_3)_2\text{CHCH}_2\text{O}-$, $(\text{CH}_3\text{CH}_2)(\text{CH}_3)_2\text{CO}-$, cyclohexyl-O-, and cyclopentyl-O-.

32. The composition of Embodiment 1 wherein: E_1 is selected from the group consisting of:

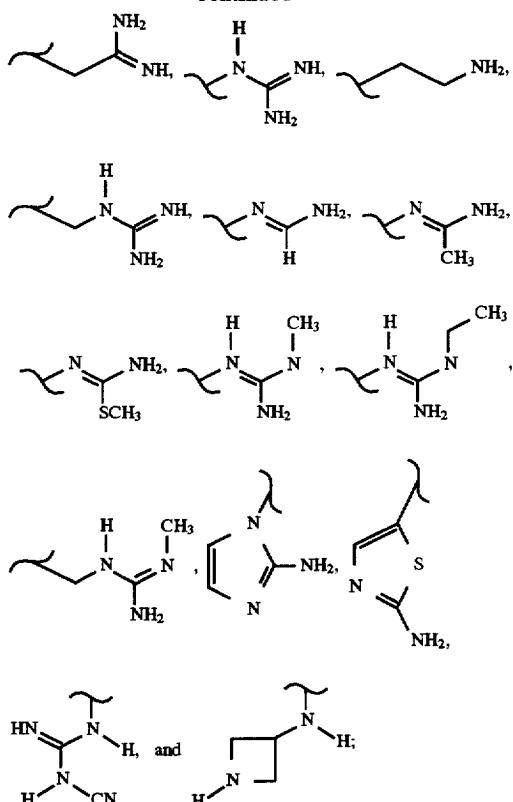


G_1 is selected from the group consisting of:



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and U_1 is an O-alkyl of 1 to 12 carbon atoms, O-alkenyl of 2 to 12 carbon atoms, or O-alkynyl of 2 to 12 carbon atoms and U_1 is substituted with 0 to 3 groups selected from the group consisting of F, Cl, Br, I, $-\text{CN}$, NO_2 , N_3 , $-\text{OR}_{6a}$, $-\text{NR}_{6b}\text{R}_{6b}$, $-\text{SR}_{6a}$, $-\text{O}-\text{C}(\text{O})\text{R}_{6a}$, or $-\text{NR}_{6b}-\text{C}(\text{O})\text{R}_{6a}$.

33. The composition of Embodiment 32 wherein if R_3 is present it is not OR_{6a} .

34. The composition of Embodiment 32 wherein U_1 is selected from $\text{CH}_3(\text{CH}_2)_4\text{O}-$, $\text{CH}_3(\text{CH}_2)_3\text{O}-$, $\text{CH}_3(\text{CH}_2)_2\text{O}-$, $(\text{CH}_3\text{CH}_2)_2\text{CHO}-$, $(\text{CH}_3\text{CH}_2)(\text{CH}_3)\text{CHO}-$, $(\text{CH}_3)_2\text{CHO}-$, $(\text{CH}_3)_2\text{CHCH}_2\text{O}-$, $(\text{CH}_3\text{CH}_2)(\text{CH}_3)_2\text{CO}-$, cyclohexyl-O- or cyclopentyl-O-.

35. The composition of Embodiment 32 wherein U_1 is alkoxy or alkoxyalkyl containing C_3-C_{12} .

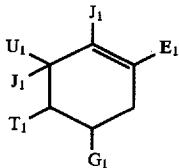
36. The composition of Embodiment 1 further comprising a pharmaceutically-acceptable carrier.

37. The composition of Embodiment 1 which has formula (I).

38. A method of inhibiting the activity of neuraminidase comprising the step of contacting a sample suspected of containing neuraminidase with the composition of Embodiment 1.

39. The method of Embodiment 20 wherein the neuraminidase is influenza neuraminidase in vivo.

40. The composition of Embodiment 1 comprising a compound of the formula:



wherein:

each J_1 is H;

E_1 is $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}_{10}$;

G_1 is $-\text{N}(\text{R}_{11})_2$, $-\text{N}(\text{R}_{11})\text{C}(\text{N}(\text{R}_{11}))(\text{N}(\text{R}_{11})_2)$, or $-\text{C}(\text{R}_{11})_2-\text{N}(\text{R}_{11})_2$;

T_1 is $-\text{N}(\text{R}_{11})(\text{C}(\text{O})\text{CH}_3)$, $-\text{N}(\text{R}_{11})(\text{C}(\text{O})\text{CH}_2\text{F})$, $-\text{N}(\text{R}_{11})(\text{C}(\text{O})\text{CHF}_2)$, or $-\text{N}(\text{R}_{11})(\text{C}(\text{O})\text{CF}_3)$;

R_{10} is alkyl of 1 to 12 carbon atoms, or alkenyl or alkynyl of 2 to 12 carbon atoms any of which is substituted with 0 to 3 R_2 ; and

each R_{11} is independently H or R_{10} .

41. The compound of Embodiment 40 wherein:

G_1 is $-\text{NH}_2$, $-\text{N}(\text{H})\text{C}(\text{N}(\text{H}))(\text{NH}_2)$, or $-\text{CH}_2-\text{NH}_2$; and

T_1 is $-\text{N}(\text{H})(\text{C}(\text{O})\text{CH}_3)$, $-\text{N}(\text{H})(\text{C}(\text{O})\text{CH}_2\text{F})$, $-\text{N}(\text{H})(\text{C}(\text{O})\text{CHF}_2)$, or $-\text{N}(\text{H})(\text{C}(\text{O})\text{CF}_3)$.

42. The compound of Embodiment 40 wherein:

R_{10} is alkyl of 1 to 12 carbon atoms, or alkenyl or alkynyl of 2 to 12 carbon atoms.

43. The compound of Embodiment 40 wherein:

R_{10} is alkyl of 1 to 8 carbon atoms, or alkenyl or alkynyl of 2 to 8 carbon atoms.

44. The compound of Embodiment 40 wherein:

R_{10} is alkyl of 1 to 6 carbon atoms, or alkenyl or alkynyl of 2 to 6 carbon atoms.

45. The compound of Embodiment 40 wherein R_{10} is alkyl of 1 to 6 carbon atoms.

46. The compound of Embodiment 40 wherein R_{10} is alkyl of 1 to 6 carbon atoms and each R_{11} is H.

47. The compound of Embodiment 40 wherein X_1 is $-\text{O}-$, $-\text{NR}_{11}-$, or $-\text{S}-$.

48. The compound of Embodiment 41 wherein X_1 is $-\text{O}-$, $-\text{NH}-$, or $-\text{S}-$.

49. The compound of Embodiment 40 wherein W_6 is $-\text{R}_5$, $-\text{W}_5$, or $-\text{R}_{5a}\text{W}_5$.

50. The compound of Embodiment 40 wherein:

W_6 is $-\text{R}_4$, $-\text{R}_{12}$, or $-\text{R}_{5a}-\text{R}_{12}$;

R_4 is an alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, alkynyl of 2 to 12 carbon atoms;

R_{12} is a cycloalkyl of 3 to 10 carbon atoms, or cycloalkenyl of 4 to 10 carbon atoms;

R_{5a} is an alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, alkynylene of 2 to 12 carbon atoms; and

with the proviso that W_6 is independently substituted with 0 to 3 R_3 or R_1 groups not H.

51. The compound of Embodiment 40 wherein:

R_3 is $-\text{Cl}$, $-\text{F}$, $-\text{N}_3$, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{11}$, $-\text{N}(\text{R}_{11})_2$, $-\text{SR}_{11}$, $-\text{S}(\text{O})\text{R}_{11}$, $-\text{S}(\text{O})_2\text{R}_{11}$, $-\text{CO}_2\text{R}_{11}$, $-\text{O}-\text{C}(\text{O})\text{R}_{11}$, $-\text{N}(\text{R}_{11})\text{C}(\text{O})\text{R}_{11}$.

52. The compound of Embodiment 51 wherein:

R_3 is $-\text{Cl}$, $-\text{F}$, $-\text{N}_3$, $-\text{CN}$, $-\text{NO}_2$, or $-\text{OR}_{10}$.

53. The compound of Embodiment 50 wherein:

R_4 is an alkyl of 1 to 8 carbon atoms, alkenyl of 2 to 8 carbon atoms, or alkynyl of 2 to 8 carbon atoms;

R_{12} is a cycloalkyl of 3 to 6 carbon atoms, or cycloalkenyl of 4 to 6 carbon atoms; and

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R_{5a} is an alkylene of 1 to 8 carbon atoms, alkenylene of 2 to 8 carbon atoms, or alkynylene of 2 to 8 carbon atoms.

54. The compound of Embodiment 53 wherein:

R_4 is an alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, or alkynyl of 2 to 6 carbon atoms;

R_{12} is a cycloalkyl of 3 to 6 carbon atoms, or cycloalkenyl of 4 to 6 carbon atoms; and

R_{5a} is an alkylene of 1 to 6 carbon atoms, alkenylene of 2 to 6 carbon atoms, or alkynylene of 2 to 6 carbon atoms.

55. The compound of Embodiment 54 wherein:

R_4 is an alkyl of 1 to 3 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R_{12} is a cycloalkyl of 3 to 10 carbon atoms, or cycloalkenyl of 4 to 10 carbon atoms; and

R_{5a} is an alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2 to 12 carbon atoms.

56. The compound of Embodiment 40 wherein:

X_1 is $-\text{O}-$, $-\text{NH}-$, or $-\text{S}-$;

W_6 is $-\text{R}_4$, $-\text{R}_{12}$, or $-\text{R}_{5a}-\text{R}_{12}$;

R_4 is an alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R_{12} is a cycloalkyl of 3 to 10 carbon atoms, or cycloalkenyl of 4 to 10 carbon atoms;

R_{5a} is an alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2 to 12 carbon atoms; and

with the proviso that W_6 is substituted with 0 to 3 groups selected from $-\text{Cl}$, $-\text{F}$, $-\text{N}_3$, $-\text{CN}$, $-\text{NO}_2$, or $-\text{OR}_{10}$.

57. The compound of Embodiment 56 wherein:

X_1 is $-\text{O}-$, or $-\text{NH}-$;

W_6 is an alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms; and

with the proviso that W_6 is substituted with 0 to 3 groups selected from $-\text{Cl}$, $-\text{F}$, $-\text{N}_3$, $-\text{CN}$, $-\text{NO}_2$, or $-\text{OR}_{10}$.

58. The compound of Embodiment 56 wherein:

X_1 is $-\text{O}-$, $-\text{NH}-$, or $-\text{S}-$;

W_6 is an alkyl of 5 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, alkynyl of 2 to 12 carbon atoms; and

with the proviso that W_6 is substituted with 0 to 3 groups selected from $-\text{N}_3$, $-\text{CN}$, $-\text{NO}_2$, or $-\text{OR}_{10}$; and R_{10} of $-\text{OR}_{10}$ is alkyl of 4 to 12 carbon atoms.

59. The compound of Embodiment 56 wherein:

X_1 is $-\text{O}-$, $-\text{NH}-$, or $-\text{S}-$;

W_6 is a branched alkyl of 3 to 12 carbon atoms, branched alkenyl of 4 to 12 carbon atoms, branched alkynyl of 4 to 12 carbon atoms; and

with the proviso that W_6 is substituted with 0 to 3 groups selected from $-\text{Cl}$, $-\text{F}$, $-\text{N}_3$, $-\text{CN}$, $-\text{NO}_2$, or $-\text{OR}_{10}$.

60. The compound of Embodiment 40 wherein:

W_6 is a cycloalkyl of 3 to 8 carbon atoms substituted with 0 to 3 R_4 groups; and

with the proviso that W_6 is substituted with 0 to 3 groups selected from $-\text{Cl}$, $-\text{F}$, $-\text{N}_3$, $-\text{CN}$, $-\text{NO}_2$, or $-\text{OR}_{10}$.

61. The compound of Embodiment 54 wherein R_{12} cycloalkyl is bicyclic.

62. The compound of Embodiment 61 wherein R_{12} bicyclic alkyl is spiroyl.

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63. The compound of Embodiment 60 wherein W_6 is substituted with 1 to 3 groups selected from $-\text{Cl}$, $-\text{F}$, $-\text{N}_3$, $-\text{CN}$, $-\text{NO}_2$, or $-\text{OR}_{10}$, and R_{10} of OR_{10} is alkyl of 4 to 12 carbon atoms. 5

64. The compound of Embodiment 63 wherein W_6 is substituted with 1 group selected from $-\text{Cl}$, $-\text{F}$, $-\text{N}_3$, $-\text{CN}$, $-\text{NO}_2$, or $-\text{OR}_{10}$. 10

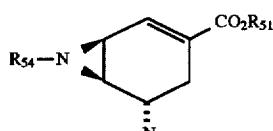
65. The compound of Embodiment 39 wherein X_1 is $-\text{O}-$; and W_6 is an alkyl of 3 to 10 carbon atoms. 10

66. The compound of Embodiment 65 wherein W_6 is branched. 15

67. The compound of Embodiment 65 wherein W_6 is an alkyl of 5 to 10 carbon atoms. 15

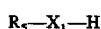
68. The compound of Embodiment 67 wherein W_6 is branched. 20

69. A method of using a compound of the formula: 20

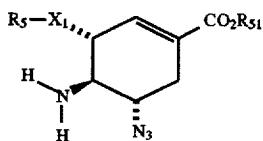


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wherein the method comprises treating compound 281 30 with a compound of the formula:



to form a compound of the formula: 35



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wherein:

X_1 is $-\text{O}-$, $-\text{NR}_5-$, or $-\text{S}-$; 45

R_1 is independently H or alkyl of 1 to 12 carbon atoms;

R_2 is independently R_3 or R_4 wherein each R_4 is independently substituted with 0 to 3 R_3 groups; 50

R_3 is independently F, Cl, Br, I, $-\text{CN}$, N_3 , $-\text{NO}_2$, $-\text{OR}_{6a}$, $-\text{OR}_1$, $-\text{N}(\text{R}_1)_2$, $-\text{N}(\text{R}_1)(\text{R}_{6b})$, $-\text{N}(\text{R}_{6b})_2$, $-\text{SR}_1$, $-\text{SR}_{6a}$, $-\text{SOR}_1$, $-\text{S}(\text{O})_2\text{R}_1$, $-\text{S}(\text{O})\text{R}_{6a}$, $-\text{S}(\text{O})_2\text{R}_{6a}$, $-\text{C}(\text{O})\text{OR}_1$, $-\text{C}(\text{O})\text{R}_{6c}$, $-\text{C}(\text{O})\text{OR}_{6a}$, $-\text{OC}(\text{O})\text{R}_1$, $-\text{NR}_1\text{C}(\text{O})\text{R}_1$, $-\text{N}(\text{R}_{6b})\text{C}(\text{O})\text{R}_1$, $-\text{C}(\text{O})\text{N}(\text{R}_1)_2$, $-\text{C}(\text{O})\text{N}(\text{R}_{6b})$ (R₁), $-\text{C}(\text{O})\text{N}(\text{R}_{6b})_2$, $-\text{C}(\text{N}\text{R}_1)(\text{N}(\text{R}_1)_2)$, $-\text{C}(\text{N}(\text{R}_{6b}))(\text{N}(\text{R}_{6b})_2)$, $-\text{N}(\text{R}_1)\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_1)_2)$, $-\text{N}(\text{R}_1)\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_{6b}))$, $-\text{N}(\text{R}_1)\text{C}(\text{N}(\text{R}_{6b}))$, $-\text{N}(\text{R}_1)(\text{R}_{6b})$, $-\text{N}(\text{R}_{6b})\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_1)_2)$, $-\text{N}(\text{R}_{6b})\text{C}(\text{N}(\text{R}_{6b}))$, $-\text{N}(\text{R}_{6b})(\text{R}_{6b})$, $-\text{N}(\text{R}_1)\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_{6b})_2)$, $-\text{N}(\text{R}_{6b})\text{C}(\text{N}(\text{R}_1))(\text{N}(\text{R}_{6b}))$, $-\text{N}(\text{R}_1)\text{C}(\text{N}(\text{R}_{6b}))(\text{N}(\text{R}_{6b})_2)$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}_{6b})$ or $=\text{N}(\text{R}_1)$; 60

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65

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R_4 is alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms; R_5 is R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups;

R_{6a} is H or a protecting group for hydroxyl or thio;

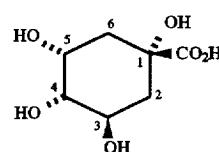
R_{6b} is H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is H or the residue of an amino-containing compound;

R_{51} is an acid stable protecting group for a carboxylic acid; and

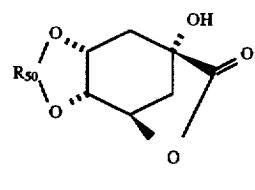
R_{54} aziridine activating group.

70. A method of using a compound of the formula:



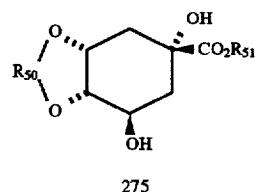
Quinic Acid

wherein the method comprises treating Quinic acid with a geminal dialkoxyalkane or geminal dialkoxy cycloalkane and acid to form a compound of the formula:



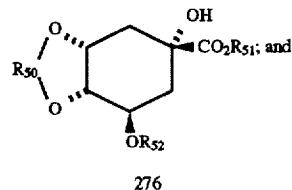
274

treating compound 274 with a metal alkoxide and an alkanol to form a compound of the formula:



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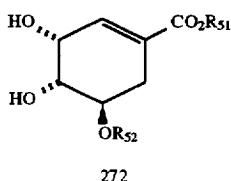
treating compound 275 with a sulfonic acid halide and an amine to form a compound of the formula:



276

treating compound 276 with a dehydrating agent followed by an acid and an alkanol to form a compound of the formula:

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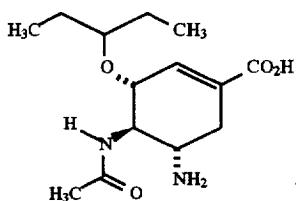
143

wherein:

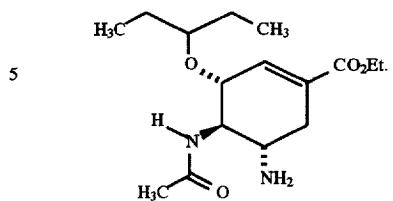
 R_{50} is a 1,2 diol protecting group; R_{51} is an acid stable carboxylic acid protecting group;
and R_{52} is a hydroxy activating group.

What is claimed is:

1. A compound of the formula:

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2. A compound of the formula:



3. A compound of claims 1 or 2 further comprising a pharmaceutically-acceptable carrier.

4. A method of inhibiting the activity of neuraminidase comprising the step of contacting a sample suspected of containing neuraminidase with a compound of claims 1 or 2.

5. The method of claim 4 wherein the neuraminidase is influenza neuraminidase *in vivo*.

6. A method for the treatment or prophylaxis of influenza infection in a host comprising administering to the host a therapeutically effective amount of a compound of claims 1 or 2.

7. The method of claim 6 wherein the compound further comprises a pharmaceutically-acceptable carrier.

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